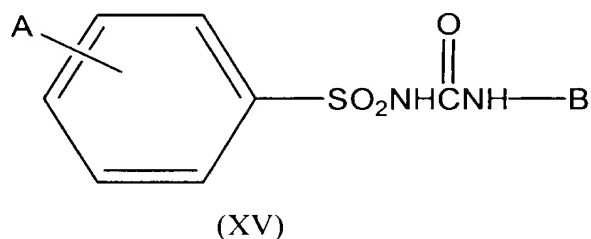We Claim:

1.   A pharmaceutical composition comprising a pharmaceutically effective amount of at least one insulin secretagogue and a pharmaceutically effective amount of at least one FBPase inhibitor.

5

2.   The pharmaceutical composition of claim 1 wherein said insulin secretagogue is a sulfonylurea antidiabetic agent.

3.   The pharmaceutical composition of claim 2 wherein said sulfonylurea
10   antidiabetic agent is a compound of formula XV:

$$A\text{—}\underset{\text{(XV)}}{\boxed{}}\text{—}SO_2NH\overset{\overset{\displaystyle O}{\|}}{C}NH\text{—}B$$

15   wherein

A is selected from hydrogen, halo, alkyl, alkanoyl, aryl, aralkyl, heteroaryl, and cycloalkyl; and

B is selected from alkyl, cycloalkyl, and heterocyclic alkyl.

20   4.   The pharmaceutical composition of claim 2 wherein said sulfonylurea antidiabetic agent is selected from glyburide, glisoxepid, acetohexamide, chlorpropamide, glibornuride, tolbutamide, tolazamide, glipizide, gliclazide, gliquidone, glyhexamide, phenbutamide, tolcyclamide, and glimepiride.

25   5.   The pharmaceutical composition of claim 1 wherein said insulin secretagogue is a non-sulfonylurea.

330

6. The pharmaceutical composition of claim 5 wherein said non-sulfonylurea is selected from mitiglinide, BTS-67582, repaglinide, and nateglinide.
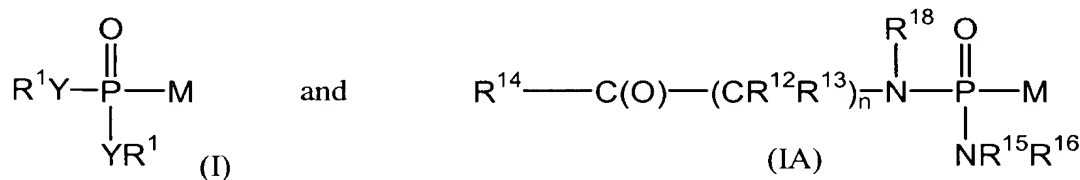
7. The pharmaceutical composition of claim 1 wherein said insulin secretagogue is a dipeptidyl peptidase-IV (DPP-IV) inhibitor.

8. The pharmaceutical composition of claim 7 wherein said dipeptidyl peptidase-IV (DPP-IV) inhibitor is selected from the group of NVP-DPP728 and P32/98.

9. The pharmaceutical composition of claim 1 wherein said insulin secretagogue is a glucagon like peptide-1 (GLP-1) receptor agonist.

10. The pharmaceutical composition of claim 9 where said glucagon like peptide-1 (GLP-1) receptor agonist is NN-2211, exendin, or an exendin agonist.

11. The pharmaceutical composition of claim 1 wherein said FBPase inhibitor is a compound selected from formulae I and IA and pharmaceutically acceptable prodrugs and salts thereof, wherein formulae I and IA are as follows:

$$R^1Y-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle YR^1}{|}}{P}}-M \quad \text{and} \quad R^{14}-C(O)-(CR^{12}R^{13})_n-\overset{\overset{\displaystyle R^{18}}{|}}{\underset{\underset{\displaystyle NR^{15}R^{16}}{|}}{N}}-\overset{\overset{\displaystyle O}{\|}}{P}-M$$

(I)   (IA)

wherein *in vivo* or *in vitro* compounds of formulae I and IA are converted to $M\text{-}PO_3{}^{2-}$, which inhibits FBPase, and wherein:
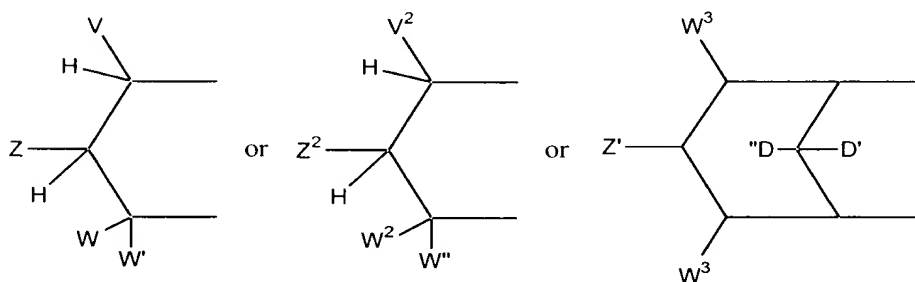
Y is independently selected from -O- and $-NR^6$, with the provisos that:

when Y is -O-, the R^1 attached to -O- is independently selected from -H, alkyl, optionally substituted aryl, optionally substituted alicyclic where the cyclic moiety contains a carbonate or a thiocarbonate, optionally substituted -arylalkyl, $-C(R^2)_2OC(O)NR^2{}_2$, $-NR^2\text{-}C(O)\text{-}R^3$, $-C(R^2)_2\text{-}OC(O)R^3$, $-C(R^2)_2\text{-}O\text{-}C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, -alkyl-S-C(O)R^3, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy;

331

when Y is $-NR^6-$, the R^1 attached to $-NR^6-$ is independently selected from $-H$, $-[C(R^2)_2]_q-COOR^3$, $-C(R^4)_2COOR^3$, $-[C(R^2)_2]_q-C(O)SR$, and -cycloalkylene-$COOR^3$, where q is 1 or 2;

when only one Y is $-O-$, which $-O-$ is not part of a cyclic group containing the other Y, the other Y is $-N(R^{18})-(CR^{12}R^{13})-C(O)-R^{14}$; and

when Y is independently selected from $-O-$ and $-NR^6$, together R^1 and R^1 are alkyl-S-S-alkyl- and form a cyclic group, or together, R^1 and R^1 form :

wherein

a)   V is selected from the group of aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkynyl and 1-alkenyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V; or

Z is selected from the group of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2aryl$, $-CH(aryl)OH$, $-CH(CH=CR^2{}_2)OH$, $-CH(C\equiv CR^2)OH$, $-R^2$, $-NR^2{}_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2NHaryl$, $-(CH_2)_p-OR^2$, and $-(CH_2)_p-SR^2$, where p is an integer 2 or 3; or

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or

W and W′ are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl and 1-alkynyl; or

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

b) V^2, W^2 and W'' are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

Z^2 is selected from the group of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OCO_2R^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OC(S)OR^3$, $-CH(aryl)OH$, $-CH(CH=CR^2_2)OH$, $-CH(C\equiv CR^2)OH$, $-SR^2$, $-CH_2NHaryl$, $-CH_2aryl$; or

together V^2 and Z^2 are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally containing 1 heteroatom, and substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from a Y attached to phosphorus;

c)   Z' is selected from the group of -OH, $-OC(O)R^3$, $-OCO_2R^3$, and $-OC(O)SR^3$;

D′ is –H;

D″ is selected from the group of -H, alkyl, $-OR^2$, -OH, and $-OC(O)R^3$;

each W^3 is independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

with the proviso that:

a)   V, Z, W, W' are not all –H and V^2, Z^2, W^2, W'' are not all –H ; and

R^2 is selected from R^3 and -H;

R^3 is selected from alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group of -H, alkylene, -alkylenearyl and aryl, or together R^4 and R^4 are connected via 2-6 atoms, optionally including one

5   heteroatom selected from the group of O, N, and S;

R^6 is selected from -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

n is an integer from 1 to 3;

R^{18} is independently selected from H, lower alkyl, aryl, and aralkyl, or, together,

10   R^{12} and R^{18} are connected via 1-4 carbon atoms to form a cyclic group;

each R^{12} and each R^{13} is independently selected from H, lower alkyl, lower aryl, lower aralkyl, all optionally substituted, or R^{12} and R^{13}, together, are connected via 2-6 carbon atoms, optionally including 1 heteroatom selected from the group of O, N, and S, to form a cyclic group;

15   each R^{14} is independently selected from -OR^{17}, -$N(R^{17})_2$, -NHR^{17}, -SR^{17}, and -NR^2R^{20};
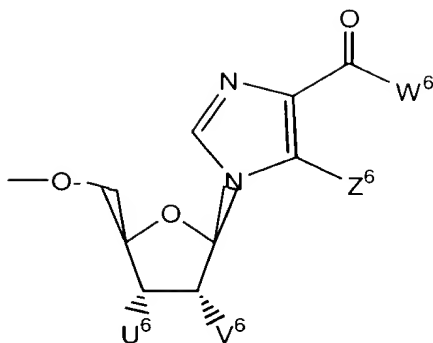
R^{15} is selected from -H, lower alkyl, lower aryl, and lower aralkyl, or, together, R^{15} and R^{16} are connected via 2-6 atoms to form a cyclic group, wherein the cyclic group optionally includes one heteroatom selected from O, N, and S;

20   R^{16} is selected from -$(CR^{12}R^{13})_n$-$C(O)$-R^{14}, -H, lower alkyl, lower aryl, and lower aralkyl, or, together, R^{15} and R^{16} are connected via 2-6 atoms to form a cyclic group, wherein the cyclic group optionally includes one heteroatom selected from O, N, and S;

each R^{17} is independently selected from lower alkyl, lower aryl, and lower aralkyl, or, when R^{14} is -$N(R^{17})_2$, together, both R^{17}s are connected via 2-6 atoms to form a cyclic

25   group, wherein the cyclic group optionally includes one heteroatom selected from O, N, and S;

R^{20} is selected from the group of -H, lower R^3, and -$C(O)$-lower R^3.

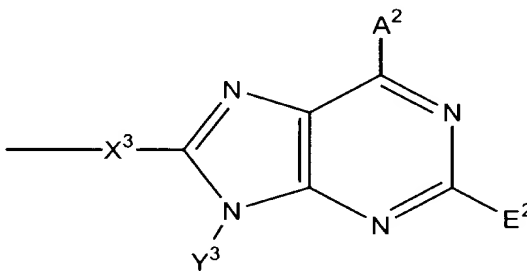12.   The pharmaceutical composition of claim 11 wherein M is:

wherein:

U^6 and V^6 are independently selected from hydrogen, hydroxy, and acyloxy, or, when taken together, U^6 and V^6 form a lower cyclic ring containing at least one oxygen;

5   W^6 is selected from amino and lower alkyl amino; and

Z^6 is selected from alkyl and halogen.

13.   The pharmaceutical composition of claim 11 wherein said insulin secretagogue is a sulfonylurea antidiabetic agent.

10

14.   The pharmaceutical composition of claim 11 wherein M is:

15   wherein:

A^2 is selected from $-NR^8_2$, $-NHSO_2R^3$, $-OR^{25}$, $-SR^{25}$, halogen, lower alkyl, $-CON(R^4)_2$, guanidine, amidine, -H, and perhaloalkyl;

E^2 is selected from -H, halogen, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-NR^7_2$;

X^3 is selected from -alkyl(hydroxy)-; -alkyl-; -alkynyl-; -aryl-; -carbonyl-alkyl-; -1,1-dihaloalkyl-; -alkoxyalkyl-; -alkyloxy-; -alkylthioalkyl-; -alkylthio-; -alkylaminocarbonyl-; -alkylcarbonylamino-; -alicyclic-; -aralkyl-; -alkylaryl-; -alkoxycarbonyl-; -carbonyloxyalkyl-; -alkoxycarbonylamino-; and

-alkylaminocarbonylamino-, all optionally substituted, with the proviso that X^3 is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2{}_2$;

Y^3 is selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2{}_2$, and $-OR^3$, all, except H, optionally substituted;

each R^4 is independently selected from $-H$ and alkyl, or, together, both R^4s form a cyclic alkyl group;

R^{25} is selected from lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

each R^7 is independently selected from -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

each R^8 is independently selected from -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or, together, both R^8s form a bidendate alkyl;
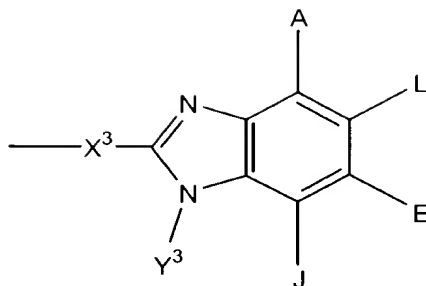
R^{10} is selected from -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from alkyl, aryl, $-NR^2{}_2$, and $-OR^2$;

and pharmaceutically acceptable prodrugs and salts thereof.

15. The pharmaceutical composition of claim 14 wherein said insulin secretagogue is a sulfonylurea antidiabetic agent.

16. The pharmaceutical composition of claim 11 wherein M is:

336

wherein:

5   A, E, and L are independently selected from $-NR^8_2$, $-NO_2$, $-H$, $-OR^7$, $-SR^7$,

$-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^{25}$, $-SO_2NR^4_2$, $-CN$,

sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5

alkynyl, and lower alicyclic, or, together, A and L form a cyclic group, or, together, L and

E form a cyclic group, or, together, E and J form a cyclic group selected from the group of

10   aryl, cyclic alkyl, and heterocyclic;

J is selected from $-NR^8_2$, $-NO_2$, $-H$, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo,

$-C(O)R^{11}$, $-CN$, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl,

haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or, together, J and Y

form a cyclic group selected from the group of aryl, cyclic alkyl, and heterocyclic alkyl;

15   X^3 is selected from -alkyl(hydroxy)-; -alkyl-; -alkynyl-; -aryl-; -carbonyl-

alkyl-; -1,1-dihaloalkyl-; -alkoxyalkyl-; -alkyloxy-; -alkylthioalkyl-; -alkylthio-;

-alkylaminocarbonyl-; -alkylcarbonylamino-; -alicyclic-; -aralkyl-; -alkylaryl-;

-alkoxycarbonyl-; -carbonyloxyalkyl-; -alkoxycarbonylamino-; and

-alkylaminocarbonylamino-, all optionally substituted, with the proviso that X^3 is not

20   substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

Y^3 is selected from $-H$, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl,

alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)$-R^{11}, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are

optionally substituted;

each R^4 is independently selected from $-H$ and alkyl, or, together, both R^4s form a
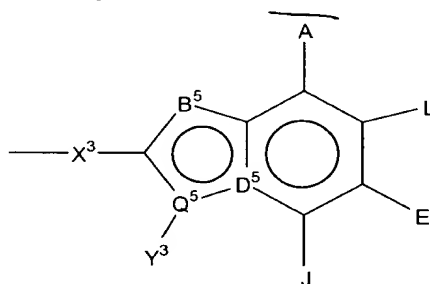
25   cyclic alkyl group;

337

R^{25} is selected from lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

each R^7 is independently selected from -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and -C(O)R^{10};

each R^8 is independently selected from -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, -C(O)R^{10}, or, together, both R^8s form a bidendate alkyl;

R^{10} is selected from -H, lower alkyl, -NH$_2$, lower aryl, and lower perhaloalkyl; and

R^{11} is selected from alkyl, aryl, -NR$^2{}_2$, and -OR^2;

and pharmaceutically acceptable prodrugs and salts thereof.

17. The pharmaceutical composition of claim 16 wherein said insulin secretagogue is a sulfonylurea antidiabetic agent.

18. The pharmaceutical composition of claim 17 wherein said sulfonylurea antidiabetic agent is selected from glyburide, glisoxepid, acetohexamide, chlorpropamide, glibornuride, tolbutamide, tolazamide, glipizide, gliclazide, gliquidone, glyhexamide, phenbutamide, tolcyclamide, and glimepiride.

19. The pharmaceutical composition of claim 16 wherein said insulin secretagogue is selected from mitiglinide, BTS-67582, repaglinide, nateglinide, dipeptidyl peptidase-IV (DPP-IV) inhibitors, and glucagon-like peptide-1 (GLP-1) receptor agonists.

20. The pharmaceutical composition of claim 11 wherein M is:

wherein:

B^5 is selected from -NH-, -N= and -CH=;

338

D^5 is selected from $-\overset{|}{C}=$ and $-\overset{|}{N}-$;

Q^5 is selected from -C= and -N-;

with the provisos that:

when B^5 is -NH-, Q^5 is -C= and D^5 is $-\overset{|}{C}=$;

when B^5 is -CH=, Q^5 is -N- and D^5 is $-\overset{|}{C}=$; and

when B^5 is -N=, D^5 is $-\overset{|}{N}-$ and Q^5 is -C=;

A, E, and L are independently selected from $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^{25}$, $-SO_2NR^4_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, and lower alicyclic, or, together, A and L form a cyclic group, or, together, L and E form a cyclic group, or, together, E and J form a cyclic group selected from the group of aryl, cyclic alkyl, and heterocyclic;

J is selected from $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group selected from the group of aryl, cyclic alkyl and heterocyclic alkyl;

X^3 is selected from -alkyl(hydroxy)-, -alkyl-, -alkynyl-, -aryl-, -carbonyl-alkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and -alkylaminocarbonylamino-, all optionally substituted; with the proviso that X^3 is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

Y^3 is selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted;

R^4 is independently selected from -H and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^{25} is selected from lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^7 is independently selected from -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and -C(O)R^{10};

R^8 is independently selected from -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, -C(O)R^{10}, or together they form a bidentate alkyl;
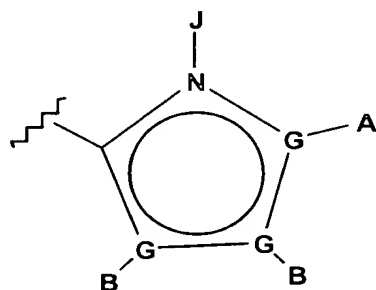
R^{10} is selected from -H, lower alkyl, -NH$_2$, lower aryl, and lower perhaloalkyl;

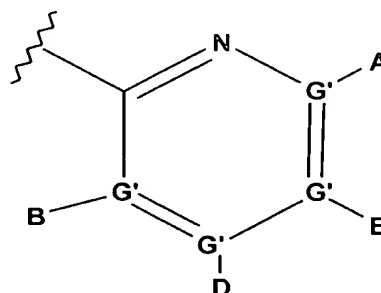R^{11} is selected from alkyl, aryl, -NR$^2_2$ and -OR^3;

and pharmaceutically acceptable prodrugs and salts thereof.

21.   The pharmaceutical composition of claim 20 wherein said insulin secretagogue is a sulfonylurea antidiabetic agent.

22.   The pharmaceutical composition of claim 11 wherein M is –X-R^5 wherein R^5 is selected from:

and

wherein:

each G is independently selected from C, N, O, S, and Se, and wherein not more than one G is O, S, or Se, and not more than one G is N;

each G' is independently selected from C and N and wherein no more than two G' groups are N;

A is selected from -H, -NR$^4_2$, -CONR$^4_2$, -CO$_2$R^3, halo, -S(O)R^3, -SO$_2$R^3, alkyl, alkenyl, alkynyl, perhaloalkyl, haloalkyl, aryl, -CH$_2$OH, -CH$_2$NR$^4_2$, -CH$_2$CN, -CN, -C(S)NH$_2$, -OR^3, -SR^3, -N$_3$, -NHC(S)NR$^4_2$, -NHAc, and null;

340

each B and D are independently selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, $-C(O)R^{11}$, $-C(O)SR^3$, $-SO_2R^{11}$, $-S(O)R^3$, -CN, $-NR^9_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, $-NO_2$, and null, all except -H, -CN, perhaloalkyl, $-NO_2$, and halo are optionally substituted;

5   E is selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, alkoxyalkyl, - $C(O)OR^3$, $-CONR^4_2$, -CN, $-NR^9_2$, $-NO_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, and null, all except -H, -CN, perhaloalkyl, and halo are optionally substituted;

J is selected from -H and null;

X is an optionally substituted linking group that links R^5 to the phosphorus atom
10   via 2-4 atoms, including 0-1 heteroatoms selected from N, O, and S, except that if X is urea or carbamate there are 2 heteroatoms, measured by the shortest path between R^5 and the phosphorus atom, and wherein the atom attached to the phosphorus is a carbon atom, and wherein X is selected from furan-2,5-diyl, -alkyl(hydroxy)-, -alkynyl-, -heteroaryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkyl-
15   thio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and -alkylaminocarbonylamino-, all optionally substituted; with the proviso that X is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

R^2 is selected from R^3 and -H;

R^3 is selected from alkyl, aryl, alicyclic, and aralkyl;

20   each R^4 is independently selected from -H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

each R^9 is independently selected from -H, alkyl, aralkyl, and alicyclic, or together R^9 and R^9 form a cyclic alkyl group or a heterocyclic group where the heteroatom is selected from the group of O,S and N;

25   R^{11} is selected from alkyl, aryl, $-NR^2_2$, and $-OR^2$;
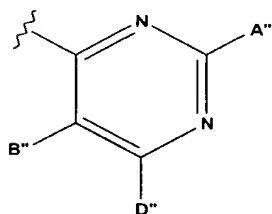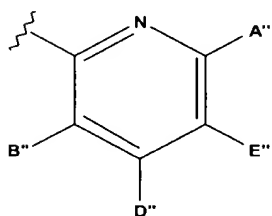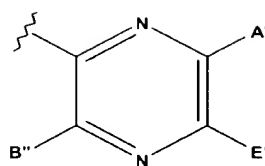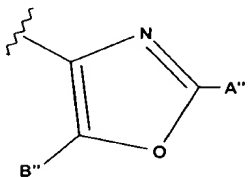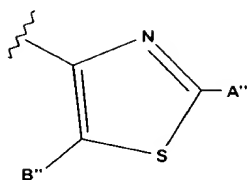
and with the proviso that:

1)   when G' is N, then the respective A, B, D, or E is null;

2)   at least one of A and B, or A, B, D, and E is not selected from -H or null;

3)   when R^5 is a six-membered ring, then X is not any 2 atom linker, an
30   optionally substituted -alkyloxy-, or an optionally substituted -alkylthio-;

4)   when G is N, then the respective A or B is not halogen or a group directly bonded to G via a heteroatom;

5)   when X is not an -aryl- group, then R^5 is not substituted with two or more aryl groups;

5   and pharmaceutically acceptable prodrugs and salts thereof.

23.   The pharmaceutical compositions of claim 22 wherein R^5 is selected from pyrrolyl; imidazolyl; oxazolyl; thiazolyl; isothiazolyl; 1,2,4-thiadiazolyl; pyrazolyl; isoxazolyl; 1,2,3-oxadiazolyl; 1,2,4-oxadiazolyl; 1,2,5-oxadiazolyl; 1,3,4-oxadiazolyl; 10   1,2,4-thiadiazolyl; 1,3,4-thiadiazolyl; pyridinyl; pyrimidinyl; pyrazinyl; pyridazinyl; 1,3,5-triazinyl; 1,2,4-triazinyl; and 1,3-selenazolyl, all of which contain at least one substituent.

24.   The pharmaceutical composition of claim 22 wherein R^5 is not 2-thiazolyl or 2-oxazolyl.

15

25.   The pharmaceutical composition of claim 22 wherein R^5 is selected from the group of:

wherein:

A" is selected from -H, -NR$^4_2$, -CONR$^4_2$, -CO$_2$R^3, halo, C$_1$-C$_6$ alkyl, C$_2$-C$_6$ alkenyl, C$_2$-C$_6$ alkynyl, C$_1$-C$_6$ perhaloalkyl, C$_1$-C$_6$ haloalkyl, aryl, -CH$_2$OH,

5   -CH$_2$NR$^4_2$, -CH$_2$CN, -CN, -C(S)NH$_2$, -OR^3, -SR^3, -N$_3$, -NHC(S)NR$^4_2$, and -NHAc;

B" and D" are independently selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, -C(O)R^{11}, -C(O)SR^3, -SO$_2$R^{11}, -S(O)R^3, -CN, -NR$^9_2$, -OR^3, -SR^3, perhaloalkyl, and halo, all except -H, -CN, perhaloalkyl, and halo are optionally substituted;

10   E" is selected from -H, C$_1$-C$_6$ alkyl, C$_2$-C$_6$ alkenyl, C$_2$-C$_6$ alkynyl, C$_4$-C$_6$ alicyclic, alkoxyalkyl, -C(O)OR^3, -CONR$^4_2$, -CN, -NR$^9_2$, -OR^3, -SR^3, C$_1$-C$_6$ perhaloalkyl, and halo, all except H, -CN, perhaloalkyl, and halo are optionally substituted; and

each R^3 is independently selected from C_1–C_6 alkyl, C_6 aryl, C_3–C_6 heteroaryl, C_3–C_8 alicyclic, C_2–C_7 heteroalicyclic, C_7–C_{10} aralkyl, and C_4–C_9 heteroaralkyl;
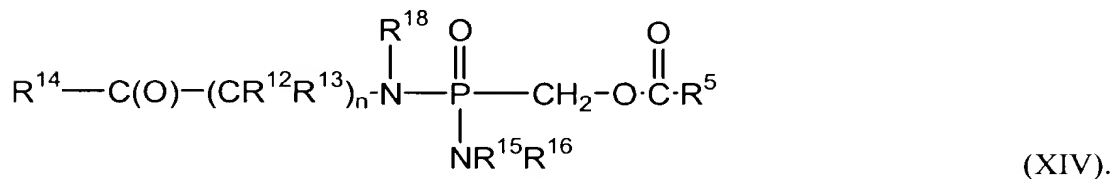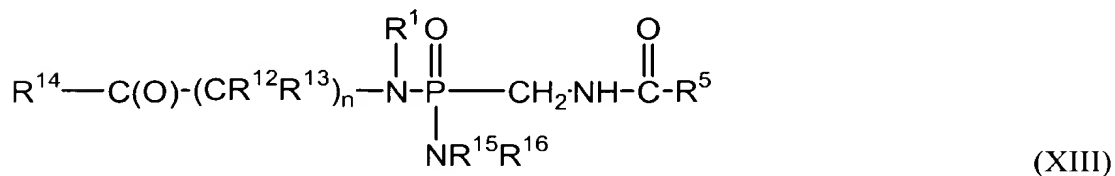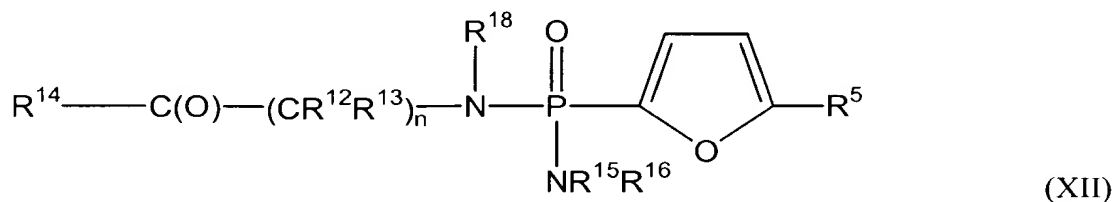
each R^4 and R^9 is independently selected from -H and C_1-C_2 alkyl;

X is selected from -heteroaryl-, -alkylcarbonylamino-, -alkylaminocarbonyl-, and -alkoxycarbonyl-;

each R^{11} is selected from -NR^4_2 , -OH, -OR^3, C_1–C_6 alkyl, C_6 aryl, and C_3–C_6 heteroaryl.

26.   The pharmaceutical composition of claim 25 wherein X is selected from -heteroaryl- and -alkoxycarbonyl-.

27.   The pharmaceutical composition of claim 25 wherein said compound is a compound of formulae XII, XIII, or XIV:

(XII)

(XIII)

(XIV).

28.   The pharmaceutical composition of claim 25 wherein:

A" is selected from -NH_2, -Cl, -Br, and -CH_3;

each B" is selected from -H, -C(O)OR^3, -C(O)SR^3, C1-C6 alkyl, alicyclic, halo, heteroaryl, and -SR^3;

D" is selected from -H, -C(O)OR^3, lower alkyl, alicyclic, and halo; and

E" is selected from -H, -Br, and -Cl.

5

29. The pharmaceutical composition of claim 27 wherein:

R^{18} is selected from -H, methyl, and ethyl;

each R^{12} and R^{13} is independently selected from -H, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, -CH$_2$CH$_2$-SCH$_3$, phenyl, and benzyl, or together R^{12} and R^{13}

10 are connected via a chain of 2-5 carbon atoms to form a cycloalkyl group;

n is 1 or 2;

each R^{14} is independently selected from -OR^{17}, wherein R^{17} is selected from methyl, ethyl, propyl, and benzyl; and

R^{15} and R^{16} are independently selected from lower alkyl and lower aralkyl, or

15 together R^{15} and R^{16} are connected via a chain of 2-6 atoms, optionally including 1 heteroatom selected from O, N, and S.

30. The pharmaceutical composition of claim 27 wherein R^{16} is -(CR^{12}R^{13})$_n$-C(O)-R^{14}.

20

31. The pharmaceutical composition of claim 27 wherein:

R^{18} is selected from -H, methyl, and ethyl;

R^{12} and R^{13} are independently selected from -H, methyl, i-propyl, i-butyl, and benzyl, or together are connected via a chain of 2-5 carbon atoms to form a cycloalkyl
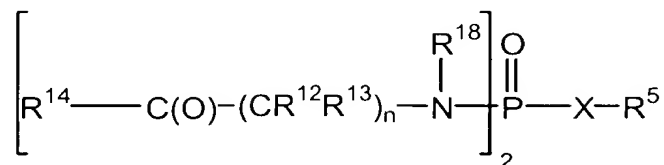
25 group;

R^{14} is -OR^{17};

R^{17} is selected from methyl, ethyl, propyl, t-butyl, and benzyl; and

R^{15} and R^{16} are independently selected from lower alkyl, and lower aralkyl, or

together R^{15} and R^{16} are connected via a chain of 2-6 atoms, optionally including 1

30 heteroatom selected from O, and N.

32.   The pharmaceutical composition of claim 22 wherein said FBPase inhibitor is a compound of the formula:

$$\left[R^{14}\!\!-\!\!C(O)\!-\!(CR^{12}R^{13})_n\!-\!N\!\!-\!\!\overset{\overset{\displaystyle R^{18}}{|}}{\underset{\,}{P}}\!\!-\!\!X\!-\!R^5 \right]_2 \quad (\text{with } O \text{ double-bonded to } P)$$

wherein X is selected from furan-2,5-diyl; -alkoxycarbonyl-; and -alkylaminocarbonyl-.

33.   The pharmaceutical composition of claim 32 wherein:

n is 1;

R^{12} and R^{13} are independently selected from -H, methyl, i-propyl, i-butyl, and benzyl, or, together, R^{12} and R^{13} are connected via a chain of 2-5 carbon atoms to form a cycloalkyl group, and, when R^{12} and R^{13} are not the same, $H_2N\text{-}CR^{12}R^{13}\text{-}C(O)\text{-}R^{14}$ is an ester or thioester of a naturally occurring amino acid;

R^{14} is selected from -OR^{17} and -SR^{17};

R^{17} is selected from methyl, ethyl, propyl, t-butyl, and benzyl; and

R^{18} is selected from -H, methyl, and ethyl.

34.   The pharmaceutical composition of claim 25 wherein:

R^5 is:

A" is selected from -NH$_2$, -CONH$_2$, halo, -CH$_3$, -CF$_3$, -CH$_2$-halo, -CN, -OCH$_3$, -SCH$_3$, and -H;

B" is selected from -H, -C(O)R^{11}, -C(O)SR^3, alkyl, aryl, alicyclic, halo, -CN, -SR^3, OR^3, and -NR$^9_2$; and
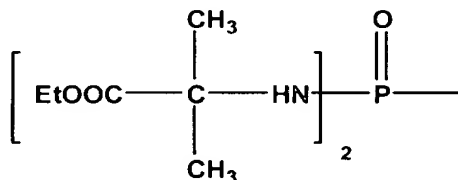
X is selected from -heteroaryl-, -alkoxycarbonyl-, and -alkylaminocarbonyl-, all optionally substituted.
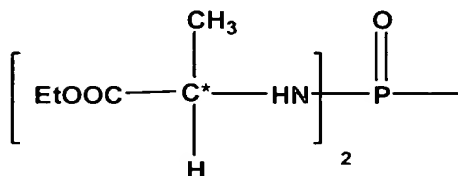
346

35.   The pharmaceutical compositions of claim 34 wherein said FBPase inhibitor is a compound of Formula 1A and wherein:

is selected from

and

wherein:

C* has S stereochemistry;

R^{18} and R^{15} are independently selected from H and methyl;

each R^{12} and R^{13} is independently selected from -H, methyl, i-propyl, i-butyl, and benzyl, or together R^{12} and R^{13} are connected via a chain of 2-5 carbon atoms to form a cycloalkyl group;

n is 1;
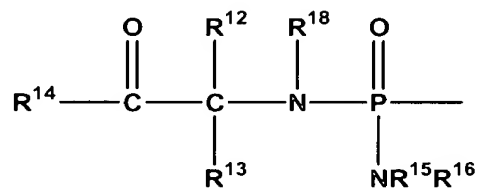
R^{14} is -OR^{17};

R^{16} is -$(CR^{12}R^{13})_n$-C(O)-R^{14}; and

R^{17} is selected from methyl, ethyl, propyl, phenyl, and benzyl.
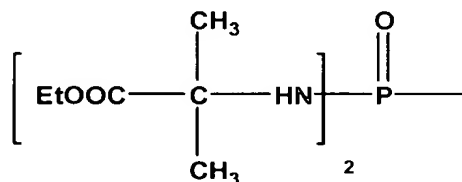
36.   The pharmaceutical composition of claim 34 wherein A" is -NH_2, X is furan-2,5-diyl, and B" is -$S(CH_2)_2CH_3$.

347

37.   The pharmaceutical composition of claim 34 wherein A" is -NH$_2$, X is furan-2,5-diyl, and B" is -CH$_2$-CH(CH$_3$)$_2$.

5   38.   The pharmaceutical composition of claim 37 wherein said FBPase inhibitor is a compound of Formula 1A and wherein

$$R^{14}-\overset{\overset{\textstyle O}{\|}}{C}-\overset{\overset{\textstyle R^{12}}{|}}{\underset{\underset{\textstyle R^{13}}{|}}{C}}-\overset{\overset{\textstyle R^{18}}{|}}{N}-\overset{\overset{\textstyle O}{\|}}{\underset{\underset{\textstyle NR^{15}R^{16}}{|}}{P}}-$$

is

$$\left[EtOOC-\overset{\overset{\textstyle CH_3}{|}}{\underset{\underset{\textstyle CH_3}{|}}{C}}-HN\right]_2\overset{\overset{\textstyle O}{\|}}{P}-$$
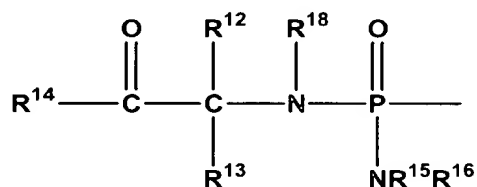
10   39.   The pharmaceutical composition of claim 37 wherein said FBPase inhibitor is a compound of Formula 1A and wherein

$$R^{14}-\overset{\overset{\textstyle O}{\|}}{C}-\overset{\overset{\textstyle R^{12}}{|}}{\underset{\underset{\textstyle R^{13}}{|}}{C}}-\overset{\overset{\textstyle R^{18}}{|}}{N}-\overset{\overset{\textstyle O}{\|}}{\underset{\underset{\textstyle NR^{15}R^{16}}{|}}{P}}-$$

15   is

$$\left[EtOOC-\overset{\overset{\textstyle CH_3}{|}}{\underset{\underset{\textstyle H}{|}}{C^*}}-HN\right]_2\overset{\overset{\textstyle O}{\|}}{P}-$$

wherein C* has S stereochemistry.

348

40.   The pharmaceutical composition of claim 22 wherein said insulin secretagogue is a sulfonylurea antidiabetic agent.
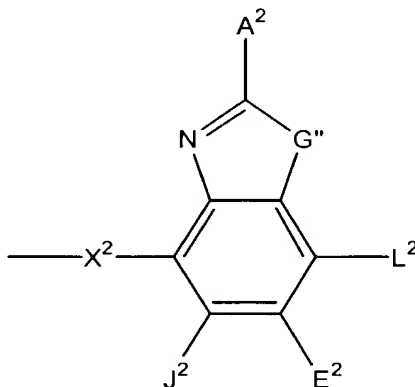
41.   The pharmaceutical composition of claim 40 wherein said sulfonylurea
5   antidiabetic agent is selected from glyburide, glisoxepid, acetohexamide, chlorpropamide, glibornuride, tolbutamide, tolazamide, glipizide, gliclazide, gliquidone, glyhexamide, phenbutamide, tolcyclamide, and glimepiride.

42.   The pharmaceutical composition of claim 22 wherein said insulin
10   secretagogue is selected from mitiglinide, BTS-67582, repaglinide, nateglinide, dipeptidyl peptidase-IV (DPP-IV) inhibitors, and glucagon like peptide-1 (GLP-1) receptor agonists.

43.   The pharmaceutical composition of claim 11 wherein M is

15

wherein:

G" is selected from -O- and -S-;

A^2, L^2, E^2, and J^2 are selected from $-NR^4_2$, $-NO_2$, -H, $-OR^2$, $-SR^2$, $-C(O)NR^4_2$, halo,

$-COR^{11}$, $-SO_2R^3$, guanidinyl, amidinyl, aryl, aralkyl, alkoxyalkyl, -SCN, $-NHSO_2R^9$,

20    $-SO_2NR^4_2$, -CN, $-S(O)R^3$, perhaloacyl, perhaloalkyl, perhaloalkoxy, C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, and lower alicyclic, or together L^2 and E^2 or E^2 and J^2 form an annulated cyclic group;

X^2 is selected from $-CR^2_2-$, $-CF_2-$, $-CR^2_2-O-$, $-CR^2_2-S-$, $-C(O)-O-$,

$-C(O)-S-$, $-C(S)-O-$, and $-CR^2_2-NR^{19}-$, and wherein in the atom attached to the

phosphorus is a carbon atom; with the proviso that X^2 is not substituted with $-COOR^2$,

$-SO_3H$, or $-PO_3R^2_2$;

5   R^2 is selected from R^3 and $-H$;

R^3 is selected from alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from $-H$, and alkyl, or together R^4 and R^4 form a

cyclic alkyl group;

each R^9 is independently selected from $-H$, alkyl, aralkyl, and alicyclic, or together

10   R^9 and R^9 form a cyclic alkyl group;

R^{11} is selected from alkyl, aryl, $-NR^2_2$, and $-OR^2$;

R^{19} is selected from lower alkyl, $-H$, and $-COR^2$;

and pharmaceutically acceptable prodrugs and salts thereof.

15   44.   The pharmaceutical composition of claim 43 wherein G" is -S-.

     45.   The pharmaceutical composition of claim 43 wherein said insulin

secretagogue is a sulfonylurea antidiabetic agent.
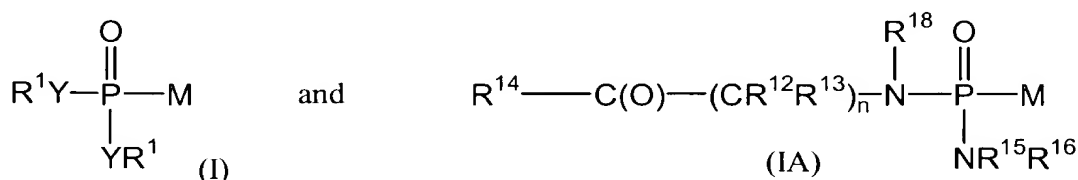

20   46.   A method of treating a mammal having diabetes comprising administering

to said mammal a pharmaceutically effective amount of a component (a) comprising at

least one insulin secretagogue and a pharmaceutically effective amount of a component (b)

comprising at least one FBPase inhibitor.

25   47.   The method of claim 46 wherein said insulin secretagogue is a sulfonylurea

antidiabetic agent.

     48.   The method of claim 47 wherein said sulfonylurea antidiabetic agent is

selected from glyburide, glisoxepid, acetohexamide, chlorpropamide, glibornuride,

30   tolbutamide, tolazamide, glipizide, gliclazide, gliquidone, glyhexamide, phenbutamide,

tolcyclamide, and glimepiride.

49.   The method of claim 46 wherein said insulin secretagogue is selected from mitiglinide, BTS-67582, replaglinide, nateglinide, dipeptidyl peptidase-IV (DPP-IV) inhibitors, and glucagon like peptide-1 (GLP-1) receptor agonists.

50.   The method of claim 46 wherein said FBPase inhibitor is a compound selected from formulae I and IA:

$$R^1Y-\overset{\displaystyle O}{\overset{\|}{\underset{\underset{\displaystyle YR^1}{|}}{P}}}-M \qquad \text{and} \qquad R^{14}-C(O)-(CR^{12}R^{13})_{\overline{n}}-\overset{\displaystyle R^{18}}{\overset{|}{\underset{\underset{\displaystyle NR^{15}R^{16}}{|}}{N}}}-\overset{\displaystyle O}{\overset{\|}{P}}-M$$

$$\text{(I)} \qquad\qquad\qquad\qquad\qquad\qquad \text{(IA)}$$

wherein *in vivo* or *in vitro* compounds of formulae I and IA are converted to $M-PO_3^{2-}$, which inhibits FBPase, and wherein:
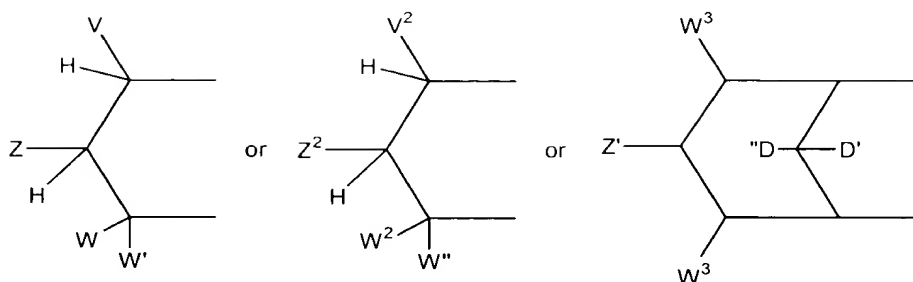
Y is independently selected from -O- and $-NR^6$, with the provisos that:

when Y is -O-, the R^1 attached to -O- is independently selected from -H, alkyl, optionally substituted aryl, optionally substituted alicyclic where the cyclic moiety contains a carbonate or a thiocarbonate, optionally substituted -arylalkyl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $-C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, -alkyl-S-C(O)R^3, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy;

when Y is $-NR^6-$, the R^1 attached to $-NR^6-$ is independently selected from -H, $-[C(R^2)_2]_q-COOR^3$, $-C(R^4)_2COOR^3$, $-[C(R^2)_2]_q-C(O)SR$, and -cycloalkylene-COOR^3, where q is 1 or 2;

when only one Y is -O-, which -O- is not part of a cyclic group containing the other Y, the other Y is $-N(R^{18})-(CR^{12}R^{13})-C(O)-R^{14}$;

when Y is independently selected from -O- and $-NR^6$, together R^1 and R^1 are alkyl-S-S-alkyl- and form a cyclic group, or together, R^1 and R^1 form :

wherein

a)   V is selected from the group of aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkynyl and 1-alkenyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V; or

Z is selected from the group of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2aryl$, $-CH(aryl)OH$, $-CH(CH=CR^2_2)OH$, $-CH(C\equiv CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2NHaryl$, $-(CH_2)_p-OR^2$, and $-(CH_2)_p-SR^2$, where p is an integer 2 or 3; or

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or

W and W' are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl and 1-alkynyl; or

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

b)　　V^2, W^2 and W'' are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

Z^2 is selected from the group of -CHR^2OH, -$CHR^2OC(O)R^3$, -$CHR^2OC(S)R^3$, -$CHR^2OCO_2R^3$, -$CHR^2OC(O)SR^3$, -$CHR^2OC(S)OR^3$, -CH(aryl)OH, -CH(CH=CR^2_2)OH, -CH(C≡CR^2)OH, -SR^2, -CH_2NHaryl, -CH_2aryl; or

together V^2 and Z^2 are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally containing 1 heteroatom, and substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from a Y attached to phosphorus;

c)　　Z' is selected from the group of -OH, -$OC(O)R^3$, -OCO_2R^3, and -$OC(O)SR^3$;

D' is -H;

D'' is selected from the group of -H, alkyl, -OR^2, -OH, and -$OC(O)R^3$;

each W^3 is independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

with the proviso that:

a)　　V, Z, W, W' are not all –H and V^2, Z^2, W^2, W'' are not all –H ;

R^2 is selected from R^3 and -H;

R^3 is selected from alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group of -H, alkylene, -alkylenearyl and aryl, or together R^4 and R^4 are connected via 2-6 atoms, optionally including one heteroatom selected from the group of O, N, and S;

R^6 is selected from -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

n is an integer from 1 to 3;

R^{18} is independently selected from H, lower alkyl, aryl, and aralkyl, or, together, R^{12} and R^{18} are connected via 1-4 carbon atoms to form a cyclic group;

each R^{12} and each R^{13} is independently selected from H, lower alkyl, lower aryl, lower aralkyl, all optionally substituted, or R^{12} and R^{13}, together, are connected via 2-6 carbon atoms, optionally including 1 heteroatom selected from the group of O, N, and S, to form a cyclic group;

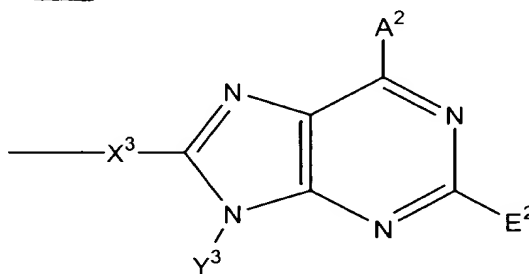each R^{14} is independently selected from $-OR^{17}$, $-N(R^{17})_2$, $-NHR^{17}$, $-SR^{17}$, and $-NR^2R^{20}$;

R^{15} is selected from -H, lower alkyl, lower aryl, and lower aralkyl, or, together, R^{15} and R^{16} are connected via 2-6 atoms to form a cyclic group, wherein the cyclic group optionally includes one heteroatom selected from O, N, and S;

R^{16} is selected from $-(CR^{12}R^{13})_n-C(O)-R^{14}$, -H, lower alkyl, lower aryl, and lower aralkyl, or, together, R^{15} and R^{16} are connected via 2-6 atoms to form a cyclic group, wherein the cyclic group optionally includes one heteroatom selected from O, N, and S;

each R^{17} is independently selected from lower alkyl, lower aryl, and lower aralkyl, or, when R^{14} is $-N(R^{17})_2$, together, both R^{17}s are connected via 2-6 atoms to form a cyclic group, wherein the cyclic group optionally includes one heteroatom selected from O, N, and S;

R^{20} is selected from the group of –H, lower R^3, and $-C(O)$-lower R^3;

and pharmaceutically acceptable prodrugs and salts thereof.

51.   The method of claim 50 wherein M is:

wherein:

A^2 is selected from -$NR^8{}_2$, $NHSO_2R^3$, -OR^{25}, -SR^{25}, halogen, lower alkyl,

-$CON(R^4)_2$, guanidine, amidine, -H, and perhaloalkyl;

E^2 is selected from -H, halogen, lower alkylthio, lower perhaloalkyl, lower alkyl,

lower alkenyl, lower alkynyl, lower alkoxy, -CN, and -$NR^7{}_2$;

5   X^3 is selected from -alkyl(hydroxy)-, -alkyl-, -alkynyl-, -aryl-, -carbonyl-

alkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-,

-alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-,

-alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and

-alkylaminocarbonylamino-, all optionally substituted; with the proviso that X^3 is not

10   substituted with -$COOR^2$, -SO_3H, or -$PO_3R^2{}_2$;

Y^3 is selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl,

alkoxyalkyl, -$C(O)R^3$, -$S(O)_2R^3$, -$C(O)$-R^{11}, -$CONHR^3$, -$NR^2{}_2$, and -OR^3, all except H

are optionally substituted;

each R^4 is independently selected from -H, and alkyl, or together R^4 and R^4 form a

15   cyclic alkyl group;

R^{25} is selected from lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^7 is independently selected from -H, lower alkyl, lower alicyclic, lower aralkyl,

lower aryl, and -$C(O)R^{10}$;

R^8 is independently selected from -H, lower alkyl, lower aralkyl, lower aryl, lower

20   alicyclic, -$C(O)R^{10}$, or together they form a bidendate alkyl;

R^{10} is selected from -H, lower alkyl, -NH_2, lower aryl, and lower perhaloalkyl;

R^{11} is selected from alkyl, aryl, -$NR^2{}_2$, and -OR^2, and

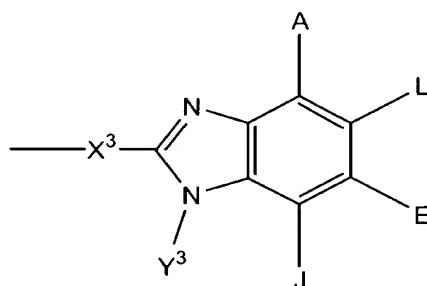pharmaceutically acceptable prodrugs and salts thereof.

25   52.   The method of claim 51 wherein said insulin secretagogue is a sulfonylurea

antidiabetic agent.

53.   The method of claim 52 wherein said sulfonylurea antidiabetic agent is

selected from glyburide, glisoxepid, acetohexamide, chlorpropamide, glibornuride,

tolbutamide, tolazamide, glipizide, gliclazide, gliquidone, glyhexamide, phenbutamide, tolcyclamide, and glimepiride.

54. The method of claim 51 wherein said insulin secretagogue is selected from
5   mitiglinide, BTS-67582, replaglinide, nateglinide, dipeptidyl peptidase-IV (DPP-IV) inhibitors, and glucagon like peptide-1 (GLP-1) receptor agonists.

55. The method of claim 50 wherein M is:

10

wherein:

A, E, and L are selected from $-NR^8_2$, $-NO_2$, $-H$, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^{25}$, $-SO_2NR^4_2$, $-CN$, sulfoxide,
15   perhaloacyl, perhaloalkyl, perhaloalkoxy, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group selected from the group of aryl, cyclic alkyl, and heterocyclic;

J is selected from $-NR^8_2$, $-NO_2$, $-H$, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, $-CN$,
20   sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group selected from the group of aryl, cyclic alkyl and heterocyclic alkyl;

X^3 is selected from -alkyl(hydroxy)-, -alkyl-, -alkynyl-, -aryl-, -carbonyl-alkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-,
25   -alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-,

356

-alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and -alkylaminocarbonylamino-, all optionally substituted; with the proviso that X^3 is not substituted with -COOR^2, -SO$_3$H, or -PO$_3$R$^2_2$;

Y^3 is selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, -C(O)R^3, -S(O)$_2$R^3, -C(O)-R^{11}, -CONHR^3, -NR$^2_2$, and -OR^3, all except H are optionally substituted;

each R^4 is independently selected from -H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^{25} is selected from lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^7 is independently selected from -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and -C(O)R^{10};

R^8 is independently selected from -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, -C(O)R^{10}, or together they form a bidendate alkyl;

R^{10} is selected from -H, lower alkyl, -NH$_2$, lower aryl, and lower perhaloalkyl;

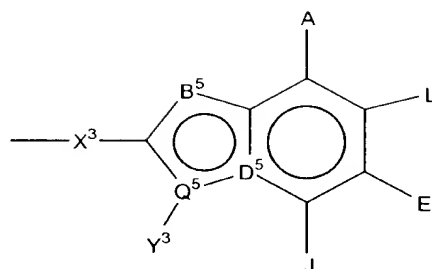R^{11} is selected from alkyl, aryl, -NR$^2_2$, and -OR^2;

and pharmaceutically acceptable prodrugs and salts thereof.

56. The method of claim 55 wherein said secretagogue is a sulfonylurea antidiabetic agent.

57. The method of claim 56 wherein said sulfonylurea antidiabetic agent is selected from glyburide, glisoxepid, acetohexamide, chlorpropamide, glibornuride, tolbutamide, tolazamide, glipizide, gliclazide, gliquidone, glyhexamide, phenbutamide, tolcyclamide, and glimepiride.

58. The method of claim 55 wherein said insulin secretagogue is selected from mitiglinide, BTS-67582, replaglinide, nateglinide, dipeptidyl peptidase-IV (DPP-IV) inhibitors, and glucagon like peptide-1 (GLP-1) receptor agonists.

59. The method of claim 50 wherein M is:

357

wherein:

B^5 is selected from -NH-, -N= and -CH=;

D^5 is selected from $-\overset{|}{C}=$ and $-\overset{|}{N}-$;

Q^5 is selected from -C= and -N-;

with the provisos that:

when B^5 is -NH-, Q^5 is -C= and D^5 is $-\overset{|}{C}=$;

when B^5 is -CH=, Q^5 is -N- and D^5 is $-\overset{|}{C}=$; and

when B^5 is -N=, then D^5 is $-\overset{|}{N}-$ and Q^5 is -C=;

A, E, and L are selected from $-NR^8{}_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4{}_2$, halo,

$-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^{25}$, $-SO_2NR^4{}_2$, -CN, sulfoxide, perhaloacyl,

perhaloalkyl, perhaloalkoxy, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, and lower

alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic

group, or together E and J form a cyclic group selected from the group of aryl, cyclic

alkyl, and heterocyclic;

J is selected from $-NR^8{}_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4{}_2$, halo, $-C(O)R^{11}$, -CN,

sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl,

aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic

group selected from the group of aryl, cyclic alkyl and heterocyclic alkyl;

X^3 is selected from -alkyl(hydroxy)-, -alkyl-, -alkynyl-, -aryl-, -carbonyl-

alkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-,

-alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-,

358

-alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and -alkylaminocarbonylamino-, all optionally substituted; with the proviso that X^3 is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

Y^3 is selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted;

each R^4 is independently selected from -H and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^{25} is selected from lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^7 is independently selected from -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidentate alkyl;

R^{10} is selected from -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from alkyl, aryl, $-NR^2_2$ and $-OR^2$; and
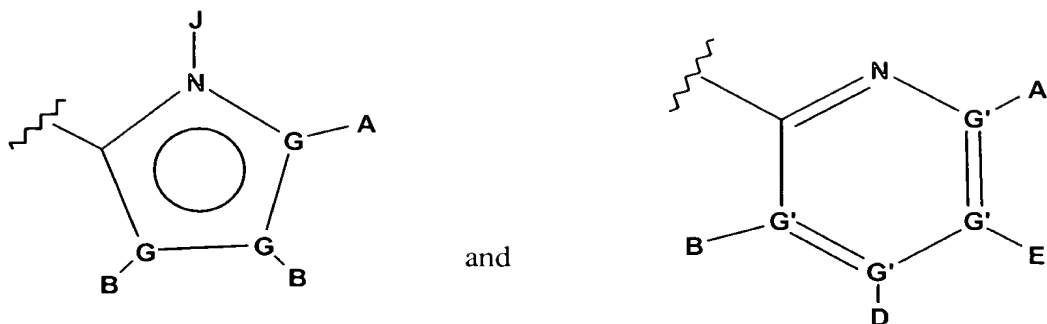
pharmaceutically acceptable prodrugs and salts thereof.

60. The method of claim 59 wherein said insulin secretagogue is a sulfonylurea antidiabetic agent.

61. The method of claim 60 wherein said sulfonylurea antidiabetic agent is selected from glyburide, glisoxepid, acetohexamide, chlorpropamide, glibornuride, tolbutamide, tolazamide, glipizide, gliclazide, gliquidone, glyhexamide, phenbutamide, tolcyclamide, and glimepiride.

62. The method of claim 59 wherein said insulin secretagogue is selected from mitiglinide, BTS-67582, replaglinide, nateglinide, dipeptidyl peptidase-IV (DPP-IV) inhibitors, and glucagon like peptide-1 (GLP-1) receptor agonists.

63. The method of claim 50 wherein M is $-X-R^5$ wherein

R^5 is selected from:

and

wherein:

each G is independently selected from C, N, O, S, and Se, and wherein not more than one G is O, S, or Se, and not more than one G is N;

each G' is independently selected from C and N and wherein no more than two G' groups are N;

A is selected from -H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, $-S(O)R^3$, $-SO_2R^3$, alkyl, alkenyl, alkynyl, perhaloalkyl, haloalkyl, aryl, $-CH_2OH$, $-CH_2NR^4_2$, $-CH_2CN$, -CN, $-C(S)NH_2$, $-OR^3$, $-SR^3$, $-N_3$, $-NHC(S)NR^4_2$, -NHAc, and null;

each B and D are independently selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, $-C(O)R^{11}$, $-C(O)SR^3$, $-SO_2R^{11}$, $-S(O)R^3$, -CN, $-NR^9_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, $-NO_2$, and null, all except -H, -CN, perhaloalkyl, $-NO_2$, and halo are optionally substituted;

E is selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, alkoxyalkyl, $-C(O)OR^3$, $-CONR^4_2$, -CN, $-NR^9_2$, $-NO_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, and null, all except -H, -CN, perhaloalkyl, and halo are optionally substituted;

J is selected from -H and null;

X is an optionally substituted linking group that links R^5 to the phosphorus atom via 2-4 atoms, including 0-1 heteroatoms selected from N, O, and S, except that if X is urea or carbamate, then there are 2 heteroatoms, measured by the shortest path between R^5 and the phosphorus atom, and wherein the atom attached to the phosphorus is a carbon atom, and wherein X is selected from -alkyl(hydroxy)-, -alkynyl-, -heteroaryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-,

-alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and -alkylaminocarbonylamino-, all optionally substituted; with the proviso that X is not substituted with -COOR^2, -SO$_3$H, or -PO$_3$R$^2_2$;
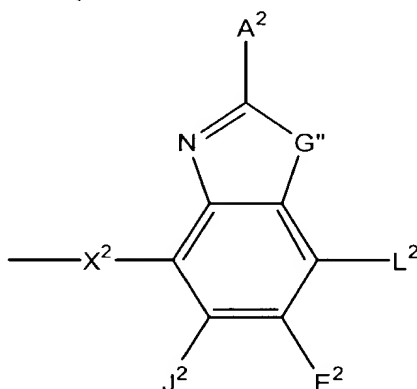
     R^2 is selected from R^3 and -H;

     R^3 is selected from alkyl, aryl, alicyclic, and aralkyl;

     each R^4 is independently selected from -H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

     each R^9 is independently selected from -H, alkyl, aralkyl, and alicyclic, or together R^9 and R^9 form a cyclic alkyl group;

     R^{11} is selected from alkyl, aryl, -NR$^2_2$, and -OR^2;

     and with the proviso that:

1)   when G' is N, then the respective A, B, D, or E is null;

2)   at least one of A and B, or A, B, D, and E is not selected from -H or null;

3)   when R^5 is a six-membered ring, then X is not a two atom linker, an optionally substituted -alkyloxy-, or an optionally substituted -alkylthio-;

4)   when G is N, then the respective A or B is not halogen or a group directly bonded to G via a heteroatom;

5)   when X is not an -aryl- group, then R^5 is not substituted with two or more aryl groups;

     and pharmaceutically acceptable prodrugs and salts thereof.

64.   The method of claim 63 wherein said insulin secretagogue is a sulfonylurea antidiabetic agent.

65.   The method of claim 64 wherein said sulfonylurea antidiabetic agent is selected from glyburide, glisoxepid, acetohexamide, chlorpropamide, glibornuride, tolbutamide, tolazamide, glipizide, gliclazide, gliquidone, glyhexamide, phenbutamide, tolcyclamide, and glimepiride.

66.   The method of claim 63 wherein said secretagogue is selected from mitiglinide, BTS-67582, replaglinide, nateglinide, dipeptidyl peptidase IV (DPP-IV) inhibitors, and glucagon like peptide-1 (GLP-1) receptor agonists.

5   67.   The method of claim 50 wherein M is:

wherein:

G" is selected from -O- and -S-;

10   A^2, L^2, E^2, and J^2 are selected from -NR^4_2, -NO_2, -H, -OR^2, -SR^2, -C(O)NR^4_2, halo,

-COR^{11}, -SO_2R^3, guanidinyl, amidinyl, aryl, aralkyl, alkoxyalkyl, -SCN, -$NHSO_2R^9$,

-$SO_2NR^4_2$, -CN, -S(O)R^3, perhaloacyl, perhaloalkyl, perhaloalkoxy, C_1-C_5 alkyl, C_2-C_5

alkenyl, C_2-C_5 alkynyl, and lower alicyclic, or together L^2 and E^2 or E^2 and J^2 form an

annulated cyclic group;

15   X^2 is selected from -CR^2_2-, -CF_2-, -CR^2_2-O-, -CR^2_2-S-, -C(O)-O-,

-C(O)-S-, -C(S)-O-, and -CR^2_2-NR^{19}-, and wherein in the atom attached to the

phosphorus is a carbon atom; with the proviso that X^2 is not substituted with -$COOR^2$,

-SO_3H, or -$PO_3R^2_2$;

R^2 is selected from R^3 and -H;

20   R^3 is selected from alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from -H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

362

each R^9 is independently selected from -H, alkyl, aralkyl, and alicyclic, or together R^9 and R^9 form a cyclic alkyl group;

R^{11} is selected from alkyl, aryl, $-NR^2_2$, and $-OR^2$;

R^{19} is selected from lower alkyl, -H, and $-COR^2$;

5   and pharmaceutically acceptable salts or prodrugs thereof.

68.   The method of claim 67 wherein said insulin secretagogue is a sulfonylurea antidiabetic agent.

10   69.   The method of claim 68 wherein said sulfonylurea antidiabetic agent is selected from glyburide, glisoxepid, acetohexamide, chlorpropamide, glibornuride, tolbutamide, tolazamide, glipizide, gliclazide, gliquidone, glyhexamide, phenbutamide, tolcyclamide, and glimepiride.

15   70.   The method of claim 67 wherein said insulin secretagogue is selected from mitiglinide, BTS-67582, replaglinide, nateglinide, dipeptidyl peptidase-IV (DPP-IV) inhibitors, and glucagon like peptide-1 (GLP-1) receptor agonists.

71.   The method of claim 46 wherein said combination is administered orally.

20

72.   The method of claim 46 wherein said disease is characterized by hyperglycemia.

73.   The method of claim 46 wherein said disease is obesity.

25

74.   The method of claim 46 wherein from about 100 mg to about 2,000 mg of said FBPase inhibitor and from about 3 mg to about 250 mg of said sulfonylurea antidiabetic agent is administered to said mammal.

75. A pharmaceutical composition comprising a pharmaceutically effective amount of insulin or insulin analogue and a pharmaceutically effective amount of an FBPase inhibitor.

76. The pharmaceutical composition of claim 75 wherein said insulin or insulin analogue is selected from insulin, insulin lispro, insulin aspart, and insulin gargline.

77. A pharmaceutical composition comprising a pharmaceutically effective amount of a biguanide and a pharmaceutically effective amount of an FBPase inhibitor.

78. The pharmaceutical composition of claim 77 wherein said biguanide is selected from metformin, phenformin, and buformin.
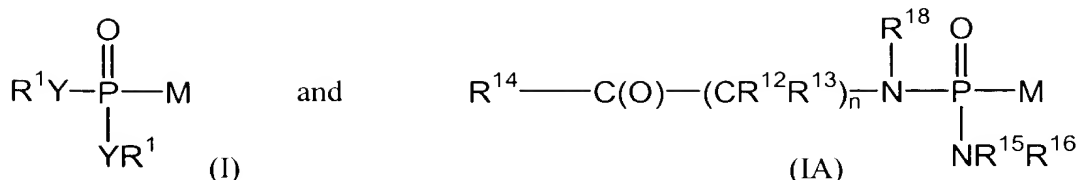
79. A pharmaceutical composition comprising a pharmaceutically effective amount of an alpha-glucosidase inhibitor and a pharmaceutically effective amount of an FBPase inhibitor.

80. The pharmaceutical composition of claim 79 wherein said alpha-glucosidase inhibitor is selected from acarbose, miglitol, and voglibose.

81. A pharmaceutical composition comprising a pharmaceutically effective amount of an FBPase inhibitor and a pharmaceutically effective amount of a hepatic glucose output inhibitor selected from glycogen phosphorylase inhibitors, glucose-6-phosphatase inhibitors, glucagon antagonists, amylin agonists, and fatty acid oxidation inhibitors.

82. The pharmaceutical composition of claim 81 wherein said amylin agonist is pramlintide.

83. The pharmaceutical composition of claim 75, 77, or 79 wherein said FBPase inhibitor is a compound selected from formulae I and IA:

$$R^1Y-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle YR^1}{|}}{P}}-M \qquad \text{and} \qquad R^{14}\text{——}C(O)-(CR^{12}R^{13})_n-\overset{\overset{\displaystyle R^{18}}{|}}{N}-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle NR^{15}R^{16}}{|}}{P}}-M$$

$$(I) \hspace{6cm} (IA)$$

wherein *in vivo* or *in vitro* compounds of formulae I and IA are converted to

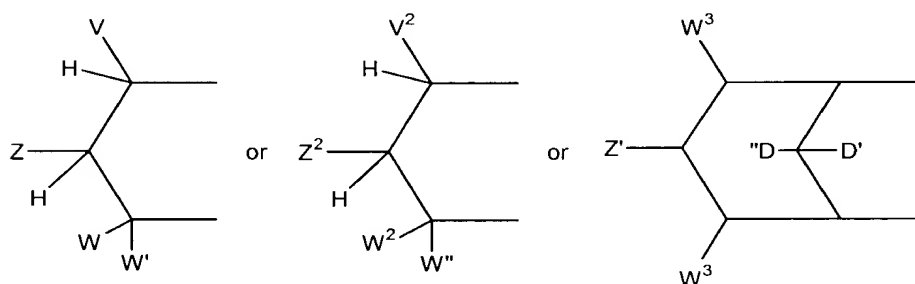$M\text{-}PO_3^{2-}$ which inhibits FBPase and wherein

Y is independently selected from -O- and $-NR^6$, with the provisos that:

5   when Y is -O-, the R^1 attached to -O- is independently selected

from -H, alkyl, optionally substituted aryl, optionally substituted alicyclic

where the cyclic moiety contains a carbonate or a thiocarbonate,

optionally substituted -arylalkyl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2\text{-}C(O)\text{-}R^3$,

$-C(R^2)_2\text{-}OC(O)R^3$, $-C(R^2)_2\text{-}O\text{-}C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$,

10   -alkyl-S-C(O)R^3, -alkyl-S-S-alkylhydroxy, and

-alkyl-S-S-S-alkylhydroxy;

     when Y is $-NR^6$-, the R^1 attached to $-NR^6$- is independently

selected from -H, $-[C(R^2)_2]_q\text{-}COOR^3$, $-C(R^4)_2COOR^3$,

$-[C(R^2)_2]_q\text{-}C(O)SR$, and -cycloalkylene-$COOR^3$, where q is 1 or 2;

15   when only one Y is -O-, which -O- is not part of a cyclic group

containing the other Y, the other Y is $-N(R^{18})\text{-}(CR^{12}R^{13})\text{-}C(O)\text{-}R^{14}$; and

     when Y is independently selected from -O- and $-NR^6$, together R^1

and R^1 are alkyl-S-S-alkyl- and form a cyclic group, or together, R^1 and R^1

form :

20

wherein

a)   V is selected from the group of aryl, substituted aryl, heteroaryl,

substituted heteroaryl, 1-alkynyl and 1-alkenyl; or

365

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V; or

Z is selected from the group of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2aryl$, $-CH(aryl)OH$, $-CH(CH=CR^2{}_2)OH$, $-CH(C\equiv CR^2)OH$, $-R^2$, $-NR^2{}_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2NHaryl$, $-(CH_2)_p-OR^2$, and $-(CH_2)_p-SR^2$, where p is an integer 2 or 3; or

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or

W and W' are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl and 1-alkynyl; or

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

b) V^2, W^2 and W'' are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

Z^2 is selected from the group of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OCO_2R^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OC(S)OR^3$, $-CH(aryl)OH$, $-CH(CH=CR^2{}_2)OH$, $-CH(C\equiv CR^2)OH$, $-SR^2$, $-CH_2NHaryl$, $-CH_2aryl$; or

together V^2 and Z^2 are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally containing 1 heteroatom, and substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or

366

aryloxycarbonyloxy attached to a carbon atom that is three atoms from a Y
attached to phosphorus;

c)   Z' is selected from the group of -OH, -OC(O)R^3, -OCO$_2$R^3, and
-OC(O)SR^3;

D' is –H;

D'' is selected from the group of -H, alkyl, -OR^2, -OH, and
-OC(O)R^3;

each W^3 is independently selected from the group of -H, alkyl,
aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-
alkenyl, and 1-alkynyl;

with the proviso that:

a)   V, Z, W, W' are not all –H and V^2, Z^2, W^2, W'' are not all
–H ;

R^2 is selected from R^3 and -H;

R^3 is selected from alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from -H, and alkyl, or together R^4 and R^4 form a
cyclic alkyl group;

R^6 is selected from -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and
lower acyl;

n is an integer from 1 to 3;

R^{18} is independently selected from H, lower alkyl, aryl, aralkyl, or together with
R^{12} is connected via 1-4 carbon atoms to form a cyclic group;

each R^{12} and R^{13} is independently selected from H, lower alkyl, lower aryl, lower
aralkyl, all optionally substituted, or R^{12} and R^{13} together are connected via 2-6 carbon
atoms to form a cyclic group;

each R^{14} is independently selected from -OR^{17}, -N(R^{17})$_2$, -NHR^{17}, and -SR^{17};

R^{15} is selected from -H, lower alkyl, lower aryl, lower aralkyl, or together with R^{16}
is connected via 2-6 atoms, optionally including 1 heteroatom selected from O, N, and S;

367

R^{16} is selected from -$(CR^{12}R^{13})_n$-C(O)-R^{14}, lower alkyl, lower aryl, lower aralkyl, or together with R^{15} is connected via 2-6 atoms, optionally including 1 heteroatom selected from O, N, and S;

each R^{17} is independently selected from lower alkyl, lower aryl, and lower aralkyl, or together R^{17} and R^{17} on N is connected via 2-6 atoms, optionally including 1 heteroatom selected from O, N, and S;
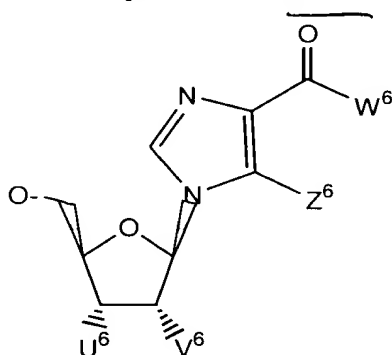
and pharmaceutically acceptable prodrugs and salts thereof.

84.   The pharmaceutical composition of claim 83 wherein said composition comprises insulin or an insulin analogue selected from insulin, insulin lispro, insulin aspart, and insulin gargline.

85.   The pharmaceutical composition of claim 83 wherein said composition comprises a biguanide selected from metformin, phenformin, and buformin.

86.   The pharmaceutical composition of claim 83 wherein said composition comprises an alpha-glucosidase inhibitor selected from acarbose, miglitol, and voglibose.

87.   The pharmaceutical composition of claim 83 wherein M is:
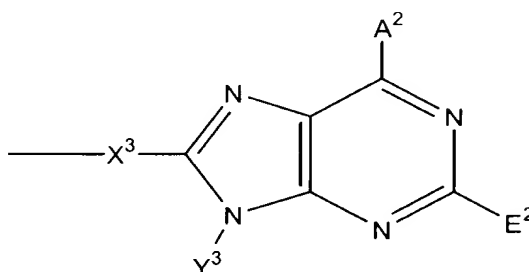

wherein

Z^6 is selected from alkyl or halogen;

U^6 and V^6 are independently selected from hydrogen, hydroxy, acyloxy or when taken together form a lower cyclic ring containing at least one oxygen;

W^6 is selected from amino and lower alkyl amino;

368

and pharmaceutically acceptable prodrugs and salts thereof.

88.   The pharmaceutical composition of claim 83 wherein M is:

5

wherein:

A^2 is selected from $-NR^8_2$, $NHSO_2R^3$, $-OR^{25}$, $-SR^{25}$, halogen, lower alkyl,

$-CON(R^4)_2$, guanidine, amidine, -H, and perhaloalkyl;

10   E^2 is selected from -H, halogen, lower alkylthio, lower perhaloalkyl, lower alkyl,

lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-NR^7_2$;

X^3 is selected from -alkyl(hydroxy)-, -alkyl-, -alkynyl-, -aryl-, -carbonyl-

alkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-,

-alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-,

15   -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and

-alkylaminocarbonylamino-, all optionally substituted; with the proviso that X^3 is not

substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

Y^3 is selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl,

alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H

20   are optionally substituted;

each R^4 is independently selected from –H and alkyl, or together R^4 and R^4 form a

cyclic alkyl group;

R^{25} is selected from lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;
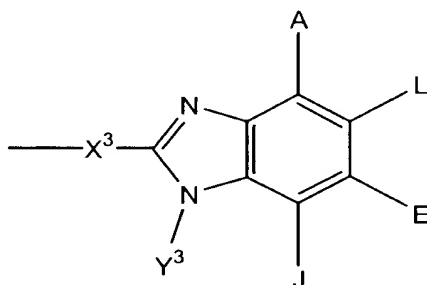
R^7 is independently selected from -H, lower alkyl, lower alicyclic, lower aralkyl,

25   lower aryl, and $-C(O)R^{10}$;

369

R^8 is independently selected from -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, -C(O)R^{10}, or together they form a bidendate alkyl;

R^{10} is selected from -H, lower alkyl, -NH$_2$, lower aryl, and lower perhaloalkyl; and

R^{11} is selected from alkyl, aryl, -NR$^2_2$, and –OR^2, and pharmaceutically acceptable

5   prodrugs and salts thereof.

89.   The pharmaceutical composition of claim 83 wherein M is:

10

wherein:

A, E, and L are selected from -NR$^8_2$, -NO$_2$, -H, -OR^7, -SR^7, -C(O)NR$^4_2$, halo, –COR^{11}, -SO$_2$R^3, guanidine, amidine, -NHSO$_2$R^{25}, -SO$_2$NR$^4_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl,

15   and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

J is selected from -NR$^8_2$, -NO$_2$, -H, -OR^7, -SR^7, -C(O)NR$^4_2$, halo, -C(O)R^{11}, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl,

20   aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl and heterocyclic alkyl;

X^3 is selected from -alkyl(hydroxy)-, -alkyl-, -alkynyl-, -aryl-, -carbonyl-alkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-,

25   -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and

-alkylaminocarbonylamino-, all optionally substituted; with the proviso that X^3 is not substituted with -COOR^2, -SO$_3$H, or -PO$_3$R$^2{}_2$;

Y^3 is selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, -C(O)R^3, -S(O)$_2$R^3, -C(O)-R^{11}, -CONHR^3, -NR$^2{}_2$, and -OR^3, all except H are

5   optionally substituted;

R^4 is independently selected from –H and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^{25} is selected from lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^7 is independently selected from -H, lower alkyl, lower alicyclic, lower aralkyl,
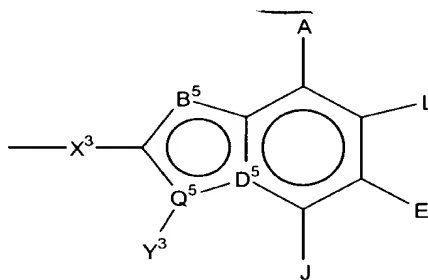
10   lower aryl, and -C(O)R^{10};

R^8 is independently selected from -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, -C(O)R^{10}, or together they form a bidendate alkyl;

R^{10} is selected from -H, lower alkyl, -NH$_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from alkyl, aryl, -NR$^2{}_2$, and –OR^2, and

15   pharmaceutically acceptable prodrugs and salts thereof.

90.   The pharmaceutical composition of claim 87 wherein M is:

20   wherein:

B^5 is selected from -NH-, -N= and -CH=;

D^5 is selected from $-\overset{|}{C}=$ and $-\overset{|}{N}-$;

Q^5 is selected from -C= and -N-;

with the provisos that:

when B^5 is -NH-, Q^5 is -C= and D^5 is $-\overset{|}{C}=$;

5   when B^5 is -CH=, Q^5 is -N- and D^5 is $-\overset{|}{C}=$; and

when B^5 is -N=, D^5 is $-\overset{|}{N}-$ and Q^5 is -C=;

A, E, and L are selected from $-NR^8{}_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4{}_2$, halo,

$-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^{25}$, $-SO_2NR^4{}_2$, -CN, sulfoxide,

perhaloacyl, perhaloalkyl, perhaloalkoxy, C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, and

10   lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic

group, or together E and J form a cyclic group including aryl, cyclic alkyl, and

heterocyclic;

J is selected from $-NR^8{}_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4{}_2$, halo, $-C(O)R^{11}$, -CN,

sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl,

15   aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic

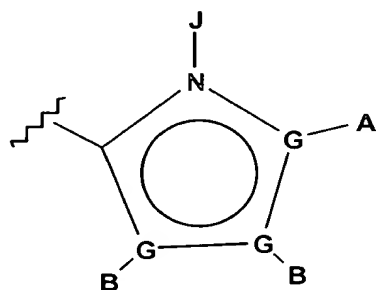group including aryl, cyclic alkyl and heterocyclic alkyl;

X^3 is selected from -alkyl(hydroxy)-, -alkyl-, -alkynyl-, -aryl-, -carbonyl-

alkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-,

-alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-,

20   -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and

-alkylaminocarbonylamino-, all optionally substituted; with the proviso that X^3 is not

substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2{}_2$;

Y^3 is selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl,

alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2{}_2$, and $-OR^3$, all except H are
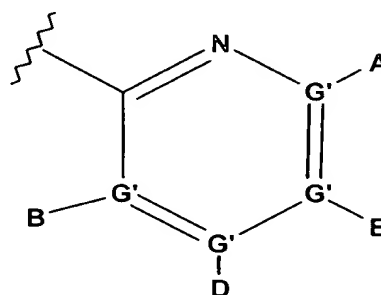
25   optionally substituted;

R^4 is independently selected from -H and alkyl, or together R^4 and R^4 form a

cyclic alkyl group;

372

R^{25} is selected from lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^7 is independently selected from -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and -C(O)R^{10};

R^8 is independently selected from -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, -C(O)R^{10}, or together they form a bidentate alkyl;

R^{10} is selected from -H, lower alkyl, -NH$_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from alkyl, aryl, -NR$^2_2$ and -OR^3; and

pharmaceutically acceptable prodrugs and salts thereof.

91.   The pharmaceutical composition of claim 83 wherein M is $-X-R^5$, wherein R^5 is selected from:

and

wherein:

each G is independently selected from C, N, O, S, and Se, and wherein only one G is O, S, or Se, and at most one G is N;

each G' is independently selected from C and N and wherein no more than two G' groups are N;

A is selected from -H, -NR$^4_2$, -CONR$^4_2$, -CO$_2$R^3, halo, -S(O)R^3, -SO$_2$R^3, alkyl, alkenyl, alkynyl, perhaloalkyl, haloalkyl, aryl, -CH$_2$OH, -CH$_2$NR$^4_2$, -CH$_2$CN, -CN, -C(S)NH$_2$, -OR^3, -SR^3, -N$_3$, -NHC(S)NR$^4_2$, -NHAc, and null;

each B and D are independently selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, -C(O)R^{11}, -C(O)SR^3, -SO$_2$R^{11}, -S(O)R^3, -CN, -NR$^9_2$, -OR^3, -SR^3, perhaloalkyl, halo, -NO$_2$, and null, all except -H, -CN, perhaloalkyl, -NO$_2$, and halo are optionally substituted;

373

E is selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, alkoxyalkyl,
-C(O)OR^3, -CONR$^4_2$, -CN, -NR$^9_2$, -NO$_2$, -OR^3, -SR^3, perhaloalkyl, halo, and null, all
except -H, -CN, perhaloalkyl, and halo are optionally substituted;

J is selected from -H and null;

X is an optionally substituted linking group that links R^5 to the phosphorus atom
via 2-4 atoms, including 0-1 heteroatoms selected from N, O, and S, except that if X is
urea or carbamate there are two heteroatoms, measured by the shortest path between R^5
and the phosphorus atom, and wherein the atom attached to the phosphorus is a carbon
atom, and wherein X is selected from -alkyl(hydroxy)-, -alkynyl-, -heteroaryl-,
-carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-,
-alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-,
-alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and
-alkylaminocarbonylamino-, all optionally substituted; with the proviso that X is not
substituted with -COOR^2, -SO$_3$H, or -PO$_3$R$^2_2$;

R^2 is selected from R^3 and -H;

R^3 is selected from alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from -H, and alkyl, or together R^4 and R^4 form a
cyclic alkyl group;

each R^9 is independently selected from -H, alkyl, aralkyl, and alicyclic, or together
R^9 and R^9 form a cyclic alkyl group;
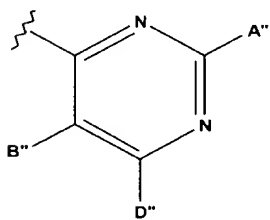
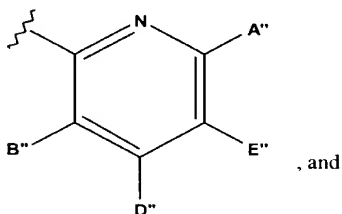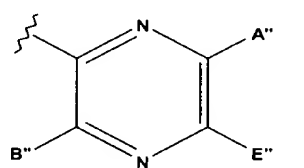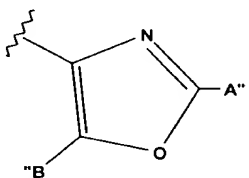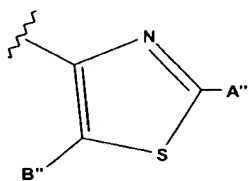R^{11} is selected from alkyl, aryl, -NR$^2_2$, and -OR^2;

and with the proviso that:

1)   when G' is N, then the respective A, B, D, or E is null;

2)   at least one of A and B, or A, B, D, and E is not selected from -H or null;

3)   when R^5 is a six-membered ring, then X is not a two atom linker, an
        optionally substituted -alkyloxy-, or an optionally substituted -alkylthio-;

4)   when G is N, then the respective A or B is not halogen or a group directly
        bonded to G via a heteroatom;

5)   when X is not an -aryl- group, then R^5 is not substituted with two or more
        aryl groups;

and pharmaceutically acceptable prodrugs and salts thereof.

374

92.   The pharmaceutical composition of claim 91 wherein R^5 is selected from
pyrrolyl, imidazolyl, oxazolyl, thiazolyl, isothiazolyl, 1,2,4-thiadiazolyl, pyrazolyl,
isoxazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl,

5   1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl,
1,3,5–triazinyl, 1,2,4-triazinyl, and 1,3-selenazolyl, all of which contain at least one
substituent.

93.   The pharmaceutical composition of claim 92 wherein R^5 is selected from:

10

wherein:

A" is selected from -H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perhaloalkyl, C_1-C_6 haloalkyl, aryl, $-CH_2OH$, $-CH_2NR^4_2$, $-CH_2CN$, -CN, $-C(S)NH_2$, $-OR^3$, $-SR^3$, $-N_3$, $-NHC(S)NR^4_2$, and -NHAc;

B" and D" are independently selected from -H, alkyl, alkenyl, alkynyl, aryl,

5   alicyclic, aralkyl, alkoxyalkyl, $-C(O)R^{11}$, $-C(O)SR^3$, $-SO_2R^{11}$, $-S(O)R^3$, -CN, $-NR^9_2$, $-OR^3$, $-SR^3$, perhaloalkyl, and halo, all except -H, -CN, perhaloalkyl, and halo are optionally substituted;

E" is selected from -H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_4-C_6 alicyclic, alkoxyalkyl, $-C(O)OR^3$, $-CONR^4_2$, -CN, $-NR^9_2$, $-OR^3$, $-SR^3$, C_1-C_6 perhaloalkyl, and halo,

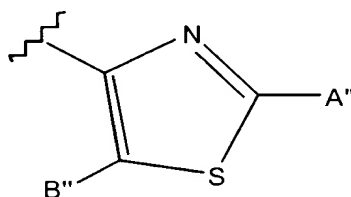10   all except H, -CN, perhaloalkyl, and halo are optionally substituted; and

each R^3 is independently selected from $C_1 - C_6$ alkyl, C_6 aryl, $C_3 - C_6$ heteroaryl, $C_3 - C_8$ alicyclic, $C_2 - C_7$ heteroalicyclic, $C_7 - C_{10}$ aralkyl, and $C_4 -C_9$ heteroaralkyl;

each R^4 and R^9 is independently selected from -H and C_1-C_2 alkyl;

X is selected from –heteroaryl-, -alkylcarbonylamino-, -alkylaminocarbonyl-, and

15   –alkoxycarbonyl-;

each R^{11} is selected from $-NR^4_2$, -OH, $-OR^3$, $C_1 - C_6$ alkyl, C_6 aryl, and $C_3 - C_6$ heteroaryl.

94.   The pharmaceutical composition of claim 93 wherein said FBPase inhibitor

20   is a compound of Formula IA and wherein R^5 is:

A" is selected from $-NH_2$, $-CONH_2$, halo, $-CH_3$, $-CF_3$, $-CH_2$-halo, -CN, $-OCH_3$, $-SCH_3$, and -H;

B" is selected from -H, $-C(O)R^{11}$, $-C(O)SR^3$, alkyl, aryl, alicyclic, halo, -CN, $-SR^3$,

25   OR^3 and $-NR^9_2$;

X is selected from -heteroaryl-, -alkoxycarbonyl-, and -alkylaminocarbonyl-,
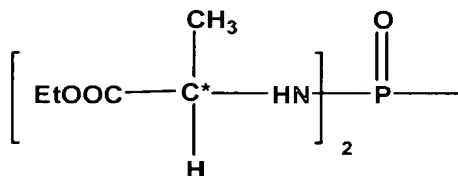all optionally substituted; and

    wherein

376

$$R^{14}-\overset{\overset{\displaystyle O}{\|}}{C}-\overset{\overset{\displaystyle R^{12}}{|}}{\underset{\underset{\displaystyle R^{13}}{|}}{C}}-\overset{\overset{\displaystyle R^{18}}{|}}{N}-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle NR^{15}R^{16}}{|}}{P}}-$$

is selected from:

$$\left[EtOOC-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}-HN \right]_2 \overset{\overset{\displaystyle O}{\|}}{P}-$$

and

$$\left[EtOOC-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle H}{|}}{C^*}}-HN \right]_2 \overset{\overset{\displaystyle O}{\|}}{P}-$$

wherein:

C* has S stereochemistry;

R^{18} and R^{15} are each independently selected from H and methyl;

each R^{12} and R^{13} is independently selected from -H, methyl, i-propyl, i-butyl, and benzyl, or, together, R^{12} and R^{13} are connected via 2-5 carbon atoms to form a cycloalkyl group;

n is 1;

R^{14} is -OR^{17};

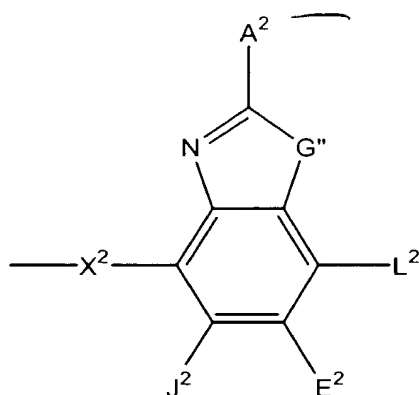R^{16} is -$(CR^{12}R^{13})_n$-C(O)-R^{14}; and

R^{17} is selected from methyl, ethyl, propyl, phenyl, and benzyl.

95.   The pharmaceutical composition of claim 94 wherein said composition comprises insulin or an insulin analogue selected from insulin, insulin lispro, insulin aspart, and insulin gargline.

96.   The pharmaceutical composition of claim 94 wherein said composition comprises a biguanide selected from metformin, phenformin, and buformin.

97.   The pharmaceutical composition of claim 94 wherein said composition comprises an alpha-glucosidase inhibitor selected from acarbose, miglitol, and voglibose.

5   98.   The pharmaceutical composition of claim 83 wherein M is:

wherein:

G" is selected from -O- and -S-;

10   A^2, L^2, E^2, and J^2 are selected from $-NR^4_2$, $-NO_2$, -H, $-OR^2$, $-SR^2$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidinyl, amidinyl, aryl, aralkyl, alkoxyalkyl, -SCN, $-NHSO_2R^9$, $-SO_2NR^4_2$, -CN, $-S(O)R^3$, perhaloacyl, perhaloalkyl, perhaloalkoxy, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, and lower alicyclic, or together L^2 and E^2 or E^2 and J^2 form an annulated cyclic group;

15   X^2 is selected from $-CR^2_2-$, $-CF_2-$, $-CR^2_2-O-$, $-CR^2_2-S-$, $-C(O)-O-$, $-C(O)-S-$, $-C(S)-O-$, and $-CR^2_2-NR^{19}-$, and wherein in the atom attached to the phosphorus is a carbon atom; with the proviso that X^2 is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

R^2 is selected from R^3 and -H;

20   R^3 is selected from alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from -H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

378

each R^9 is independently selected from -H, alkyl, aralkyl, and alicyclic, or together R^9 and R^9 form a cyclic alkyl group;

R^{11} is selected from alkyl, aryl, $-NR^2_2$, and $-OR^2$;

R^{19} is selected from lower alkyl, -H, and $-COR^2$;

5   and pharmaceutically acceptable prodrugs and salts thereof.

99.   A method of treating a mammal having diabetes comprising administering to said mammal:

a pharmaceutically effective amount of a component (a) comprising at least one of
10 an insulin, an insulin analogue, a biguanide, a hepatic glucose output inhibitor, or an alpha-glucosidase inhibitor; and

a pharmaceutically effective amount of a component (b) comprising at least one FBPase inhibitor.

15 100.   The method of claim 99 wherein said insulin or insulin analogue is selected from insulin, insulin lispro, insulin aspart, and insulin gargline.
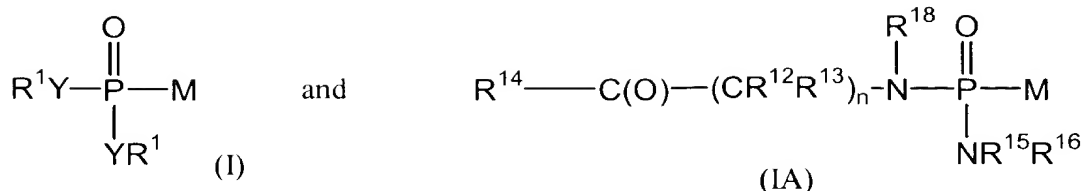
101.   The method of claim 99 wherein said biguanide is selected from metformin, phenformin, and buformin.

20

102.   The method of claim 99 wherein said hepatic glucose output inhibitor is selected from glycogen phosphorylase inhibitors, glucose-6-phosphatase inhibitors, glucagon antagonists, amylin agonists, and fatty acid oxidation inhibitors.

25 103.   The method of claim 102 wherein said amylin agonist is pramlintide.

104.   The method of claim 99 wherein said alpha-glucosidase is selected from acarbose, miglitol, and voglibose.

30 105.   The method of claim 99 wherein said FBPase inhibitor is a compound selected from formulae I and IA:

$$R^1Y-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle YR^1}{|}}{P}}-M \qquad \text{and} \qquad R^{14}-\!\!\!-C(O)-(CR^{12}R^{13})_n\text{-}N-\overset{\overset{\displaystyle R^{18}}{|}}{\underset{\underset{\displaystyle NR^{15}R^{16}}{|}}{P}}\overset{\overset{\displaystyle O}{\|}}{}\!\!\!-M$$

(I)   (IA)

wherein *in vivo* or *in vitro* compounds of formulae I and IA are converted to $M\text{-}PO_3{}^{2-}$ which inhibits FBPase and wherein
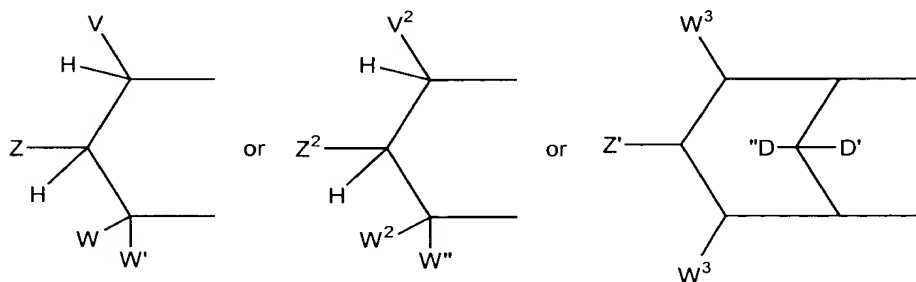
Y is independently selected from -O- and $-NR^6$, with the provisos that:

5   when Y is -O-, the R^1 attached to -O- is independently selected from -H, alkyl, optionally substituted aryl, optionally substituted alicyclic where the cyclic moiety contains a carbonate or a thiocarbonate, optionally substituted -arylalkyl, $-C(R^2)_2OC(O)NR^2{}_2$, $-NR^2\text{-}C(O)\text{-}R^3$, $-C(R^2)_2\text{-}OC(O)R^3$, $-C(R^2)_2\text{-}O\text{-}C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$,

10   -alkyl-S-C(O)R^3, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy;

when Y is $-NR^6$-, the R^1 attached to $-NR^6$- is independently selected from -H, $-[C(R^2)_2]_q\text{-}COOR^3$, $-C(R^4)_2COOR^3$, $-[C(R^2)_2]_q\text{-}C(O)SR$, and -cycloalkylene-$COOR^3$, where q is 1 or 2;

15   when only one Y is -O-, which -O- is not part of a cyclic group containing the other Y, the other Y is $-N(R^{18})\text{-}(CR^{12}R^{13})\text{-}C(O)\text{-}R^{14}$; and

when Y is independently selected from -O- and $-NR^6$, together R^1 and R^1 are alkyl-S-S-alkyl- and form a cyclic group, or together, R^1 and R^1 form :

20

wherein

a)   V is selected from the group of aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkynyl and 1-alkenyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V; or

Z is selected from the group of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2aryl$, $-CH(aryl)OH$, $-CH(CH=CR^2{}_2)OH$, $-CH(C\equiv CR^2)OH$, $-R^2$, $-NR^2{}_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2NHaryl$, $-(CH_2)_p-OR^2$, and $-(CH_2)_p-SR^2$, where p is an integer 2 or 3; or

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or

W and W' are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl and 1-alkynyl; or

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

b) V^2, W^2 and W'' are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

Z^2 is selected from the group of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OCO_2R^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OC(S)OR^3$, $-CH(aryl)OH$, $-CH(CH=CR^2{}_2)OH$, $-CH(C\equiv CR^2)OH$, $-SR^2$, $-CH_2NHaryl$, $-CH_2aryl$; or

together V^2 and Z^2 are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally containing 1 heteroatom, and substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or

381

aryloxycarbonyloxy attached to a carbon atom that is three atoms from a Y attached to phosphorus;

c)   Z' is selected from the group of -OH, -OC(O)R^3, -OCO$_2$R^3, and -OC(O)SR^3;

D' is –H;

D'' is selected from the group of -H, alkyl, -OR^2, -OH, and -OC(O)R^3;

each W^3 is independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

with the proviso that:

a)   V, Z, W, W' are not all –H and V^2, Z^2, W^2, W'' are not all –H ;

R^2 is selected from R^3 and -H;

R^3 is selected from alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from -H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^6 is selected from -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

n is an integer from 1 to 3;

R^{18} is independently selected from H, lower alkyl, aryl, aralkyl, or together with R^{12} is connected via 1-4 carbon atoms to form a cyclic group;

each R^{12} and R^{13} is independently selected from H, lower alkyl, lower aryl, lower aralkyl, all optionally substituted, or R^{12} and R^{13} together are connected via 2-6 carbon atoms to form a cyclic group;
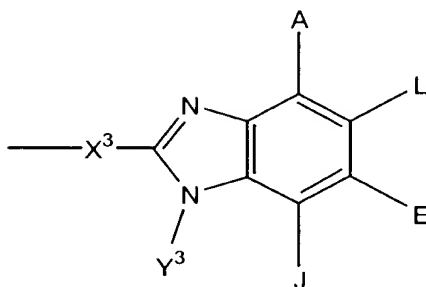
each R^{14} is independently selected from -OR^{17}, -N(R^{17})$_2$, -NHR^{17}, and -SR^{17};

R^{15} is selected from -H, lower alkyl, lower aryl, lower aralkyl, or together with R^{16} is connected via 2-6 atoms, optionally including 1 heteroatom selected from O, N, and S;

R^{16} is selected from -(CR^{12}R^{13})$_n$-C(O)-R^{14}, lower alkyl, lower aryl, lower aralkyl, or together with R^{15} is connected via 2-6 atoms, optionally including 1 heteroatom selected from O, N, and S;

382

each R^{17} is independently selected from lower alkyl, lower aryl, and lower aralkyl, or together R^{17} and R^{17} on N is connected via 2-6 atoms, optionally including 1 heteroatom selected from O, N, and S;

M comprises:

5

wherein:

A, E, and L are selected from $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^{25}$, $-SO_2NR^4_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, and

10 lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

J is selected from $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl,

15 aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl and heterocyclic alkyl;

X^3 is selected from -alkyl(hydroxy)-, -alkyl-, -alkynyl-, -aryl-, -carbonyl-alkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-,

20 -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and -alkylaminocarbonylamino-, all optionally substituted; with the proviso that X^3 is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

Y^3 is selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are

25 optionally substituted;

each R^4 is independently selected from -H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

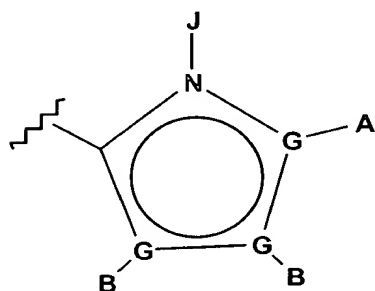R^{25} is selected from lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^7 is independently selected from -H, lower alkyl, lower alicyclic, lower aralkyl,

5   lower aryl, and -C(O)R^{10};

R^8 is independently selected from -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, -C(O)R^{10}, or together they form a bidendate alkyl;
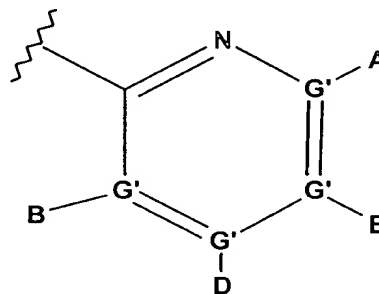
R^{10} is selected from -H, lower alkyl, -NH$_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from alkyl, aryl, -NR$^2_2$, and -OR^2, and

10   M is -X-R^5, wherein R^5 is selected from:

and

wherein:

each G is independently selected from C, N, O, S, and Se, and wherein only one G

15   is O, S, or Se, and at most one G is N;

each G' is independently selected from C and N and wherein no more than two G' groups are N;

A is selected from -H, -NR$^4_2$, -CONR$^4_2$, -CO$_2$R^3, halo, -S(O)R^3, -SO$_2$R^3, alkyl, alkenyl, alkynyl, perhaloalkyl, haloalkyl, aryl, -CH$_2$OH, -CH$_2$NR$^4_2$, -CH$_2$CN, -CN,

20   -C(S)NH$_2$, -OR^3, -SR^3, -N$_3$, -NHC(S)NR$^4_2$, -NHAc, and null;

each B and D are independently selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, -C(O)R^{11}, -C(O)SR^3, -SO$_2$R^{11}, -S(O)R^3, -CN, -NR$^9_2$, -OR^3, -SR^3, perhaloalkyl, halo, -NO$_2$, and null, all except -H, -CN, perhaloalkyl, -NO$_2$, and halo are optionally substituted;

E is selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, alkoxyalkyl, -C(O)OR^3, -CONR$^4_2$, -CN, -NR$^9_2$, -NO$_2$, -OR^3, -SR^3, perhaloalkyl, halo, and null, all except -H, -CN, perhaloalkyl, and halo are optionally substituted;

J is selected from -H and null;

5   X is an optionally substituted linking group that links R^5 to the phosphorus atom via 2-4 atoms, including 0-1 heteroatoms selected from N, O, and S, except that if X is urea or carbamate there are two heteroatoms, measured by the shortest path between R^5 and the phosphorus atom, and wherein the atom attached to the phosphorus is a carbon atom, and wherein X is selected from -alkyl(hydroxy)-, -alkynyl-, -heteroaryl-,

10   -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkyl-thio-, -alkylaminocarbonyl-, -alkylcarbonyl-amino-, -alkoxycarbonyl-, -carbonyloxy-alkyl-, -alkoxycarbonylamino-, and -alkylaminocarbonylamino-, all optionally substituted; with the proviso that X is not substituted with -COOR^2, -SO$_3$H, or -PO$_3$R$^2_2$;

R^2 is selected from R^3 and -H;

15   R^3 is selected from alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from -H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

each R^9 is independently selected from -H, alkyl, aralkyl, and alicyclic, or together R^9 and R^9 form a cyclic alkyl group;

20   R^{11} is selected from alkyl, aryl, -NR$^2_2$, and -OR^2;

and with the proviso that:
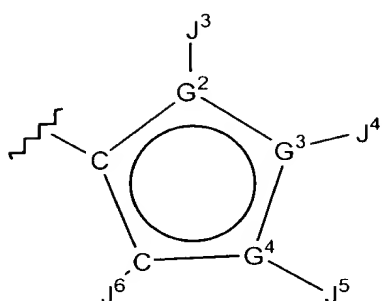
1)   when G' is N, then the respective A, B, D, or E is null;

2)   at least one of A and B, or A, B, D, and E is not selected from -H or null;

3)   when R^5 is a six-membered ring, then X is not a two atom linker, an

25   optionally substituted -alkyloxy-, or an optionally substituted -alkylthio-;

4)   when G is N, then the respective A or B is not halogen or a group directly bonded to G via a heteroatom;

5)   when X is not an -aryl- group, then R^5 is not substituted with two or more aryl groups.
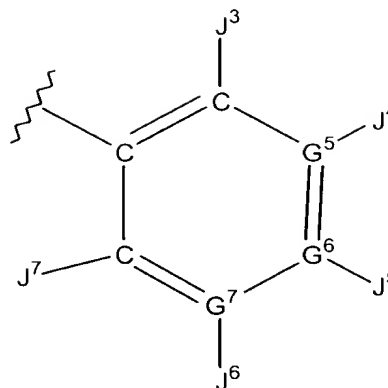
30

106.   The pharmaceutical composition of claim 11 wherein M is –X^4-R^{55}

385

wherein R^{55} is selected from:

VII-5   VII-6

wherein:

G^2 is selected from the group of C, O, and S;

G^3 and G^4 are independently selected from the group of C, N, O, and S;

wherein a) not more than one of G^2, G^3, and G^4 is O, or S; b) when G^2 is O or S, not more than one of G^3 and G^4 is N; c) at least one of G^2, G^3, and G^4 is C; and d) G^2, G^3, and G^4 are not all C;

G^5, G^6 and G^7 are independently selected from the group of C and N, wherein no more than two of G^5, G^6 and G^7 are N;

J3, J^4, J^5, J^6, and J^7 are independently selected from the group of -H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, $-S(O)_2NR^4_2$, $-S(O)R^3$, $-SO_2R^3$, alkyl, alkenyl, alkynyl, alkylenearyl, perhaloalkyl, haloalkyl, aryl, heteroaryl, alkylene-OH, $-C(O)R^{11}$, $-OR^{11}$, -alkylene-NR^4_2, -alkylene-CN, -CN, $-C(S)NR^4_2$, $-OR^2$, $-SR^2$, $-N_3$, $-NO_2$, $-NHC(S)NR^4_2$, and $-NR^{21}COR^2$;

X^4 is selected from:

i) a linking group having 2-4 atoms measured by the fewest number of atoms connecting the carbon of the aromatic ring and the phosphorus atom and is selected from the group of –furanyl-, -thienyl-, -pyridyl-, -oxazolyl-, -imidazolyl-, -phenyl-, –pyrimidinyl-, –pyrazinyl-, and -alkynyl-, all of which are optionally substituted; and

ii) a linking group having 3-4 atoms measured by the fewest number of atoms connecting the carbon of the aromatic ring and the phosphorus atom and is selected from the group of –alkylenecarbonylamino-,

386

-alkyleneaminocarbonyl-, -alkyleneoxycarbonyl-, -alkyleneoxy-, and

—alkyleneoxyalkylene-, all of which are optionally substituted;

R^{11} is selected from the group of alkyl, aryl, $-NR^2_2$, and $-OR^2$;
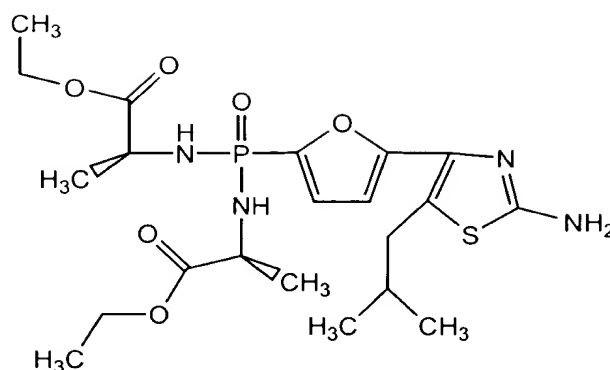
R^{20} is selected from the group of –H, lower R^3, and $-C(O)$-(lower R^3);

R^{21} is selected from –H and lower R^3;

with the provisos that:

1) when G^5, G^6, or G^7 is N, then the respective J^4, J^5, or J^6 is null;

2) when X^4 is substituted furanyl, then at least one of J^3, J^4, J^5 and J^6 is not –H or null;

3) when X^4 is not substituted furanyl, then at least two of J^3, J^4, J^5 and J^6 on formula VII-5 or J^3, J^4, J^5, J^6 and J^7 on formula VII-6 are not –H or null;

4) when G^2, G^3, or G^4 is O or S, then the respective J^3, J^4 or J^5 is null;

5) when G^3 or G^4 is N, then the respective J^4 or J^5 is not halogen or a group directly bonded to G^3 or G^4 via a heteroatom;

6) if both Y groups are $-NR^6$-, and R^1 and R^1 are not connected to form a cyclic phosphoramidate, then at least one R^1 is $-(CR^{12}R^{13})_n-C(O)-R^{14}$;

7) when X^4 is –alkylenecarbonylamino- or -alkyleneaminocarbonyl-, then G^5, G^6, and G^7 are not all C;

8) when X^4 is –alkeneoxyalkylene-, and G^5, G^6, and G^7 are all C, then neither J^4 nor J^6 can be substituted with an acylated amine;

9) when R^{55} is substituted phenyl, then J^4, J^5 and J^6 is not purinyl, purinylalkylene, deaza-purinyl, or deazapurinylalkylene;

10) R^1 can be selected from the lower alkyl only when the other YR^1 is $-NR^{18}-C(R^{12}R^{13})_n-C(O)-R^{14}$;

11) when R^{55} is substituted phenyl and X^4 is 1,2-ethynyl, then J^4 or J^6 is not a heterocyclic group;

12) when X^4 is 1,2-ethynyl, then G^5 or G^7 cannot be N;

and pharmaceutically acceptable prodrugs and salts thereof.

107. The pharmaceutical composition of claim 40, wherein said FBPase inhibitor is

Compound J.

108.   A method according to any one of claims 46 or 99, wherein said component
5   (a) and said component (b) are administered within about one hour of each other.

109.   A method according to claim 108, wherein said component (a) and said
component (b) are administered within about 10 minutes of each other.

10   110.   A method according to any one of claims 46 or 99, wherein one of said
component (a) and said component (b) is administered first and the other of said
component (a) and said component (b) is administered between 1 to 12 hours later.

111.   A method according to any one of claims 46 or 99, wherein said mammal is
15   a brittle diabetic.

112.   A method according to any one of claims 46 or 99, wherein said mammal
has NIDDM.

20   113.   A method according to any one of claims 46 or 99, wherein said mammal
has IDDM.

114.   The pharmaceutical composition of claim 9 where said glucagon like
peptide-1 (GLP-1) receptor agonist is NN-2211 or exendin.